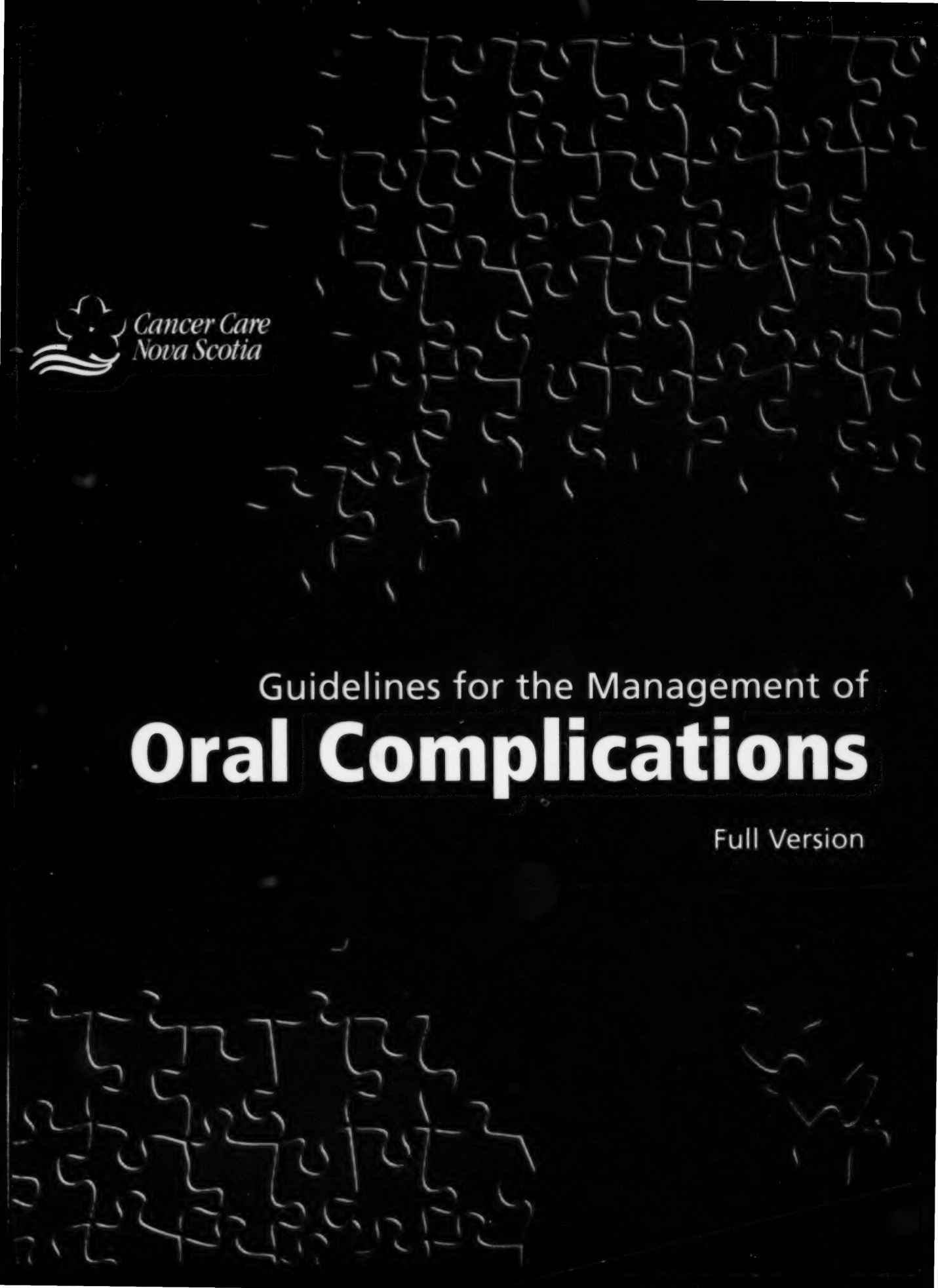

Guidelines for the Management of

Oral Complications

Full Version

2008-03184/

Cancer Care
Nova Scotia

Best Practice Guidelines for the Management of

Oral Complications from Cancer Therapy

Best Practice Guidelines for the Management of Oral Complications from Cancer Therapy

Objective:
This guideline will review assessment and management of oral complications from treatment in cancer patients, including those receiving surgery or radiotherapy to the head and neck, or chemotherapy-induced mucositis. Evidence will be reviewed and recommendations made for assessment, treatment and other management issues. A simplified discussion with flowcharts (practice pathways) will summarize the written contents. Through improved knowledge of health care professionals, it is expected that management of oral complications may be improved.

One specific objective for this guideline is to **standardize the assessment of oral complications from cancer therapy across Nova Scotia**. By creating a common approach to assessment, the authors propose we can improve the assessment and management of oral complications for cancer patients.

Preamble Note:
Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. This guideline is intended to assist health care professionals to care for cancer patients with oral complications from their treatments. Management should be customized to meet the unique needs of individuals and their families. Further information on oral complication management for children with cancer may be obtained from the IWK Health Centre Hematology-Oncology Team.

Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and health professional which are unique to each circumstance. Guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision.

This guideline will be reviewed in three years from publication date or earlier if important new evidence becomes available. Current versions of this guideline will be available on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

These guidelines are designed for health care professionals, working in a variety of settings. For front-line health care givers, the Quick Reference Version of the guidelines will be a useful reminder of assessment and treatment. This Full Version will be useful for those who prefer to read a bit more about the recommendations. The full evidence-based discussions of these guidelines are located in the Appendices of the Comprehensive Version, available on request or at the *Cancer Care Nova Scotia* website. The development of these guidelines is described in Appendix XI.

Patients, families and other non-health care professionals are recommended to review materials written for the lay public, such as the Living Well With Cancer information series.

Comment on Evidence:
There is a scarcity of clinical trial evidence on most aspects of oral complication management in cancer patients. When high-quality evidence was not available, a 'best practice' approach was used to develop this guideline. Clinicians should continue to

provide the best possible care for cancer patients, despite the absence of definitive evidence. Best practices include experience and sound clinical judgment, aided by level III & IV evidence where available, and should be given serious consideration for patient care and policy decisions.

Comment on Clinical Research:
An important component of treatment decision-making for any patient is the potential for enrollment in relevant clinical research. The Supportive Care Cancer Site Team is committed to advancing patient care, through participation in clinical trials and other clinical research projects. At any point in time, there may be a clinical trial or other clinical research opportunity related to any component of this guideline. As specific trials or clinical research projects become available, eligible patients may be offered the opportunity to enroll in the relevant trial or research project. Every effort will be made to accommodate patients for clinical research participation, but there will be eligibility restrictions for each trial. Patients are encouraged to discuss clinical research opportunities with their health care providers. Other researchers may also contact patients to offer participation in relevant trials. Current clinical trials will be listed on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca).

Acknowledgements:
This guideline was written by a collaborative effort of the Supportive Care Cancer Site Team, and was sponsored by ***Cancer Care Nova Scotia***. Background research for the treatment was performed by Sophie Goeury, pharmacy student from Nancy, France. The guidelines also incorporate knowledge of current evidence by the cancer experts in Nova Scotia.

For further information on this, or any other Practice Guideline, please contact the CST Co-Chairs, or members of the Guidelines Resource Team, ***Cancer Care Nova Scotia***.
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Part 1. Introduction

1.1 Oral Complications of Cancer

The patient with cancer faces an assault on oral health from both the disease and the treatment options. The development of oral complications can cause a variety of problems that have significant impact on the individual.

Cancers that invade the head and neck area can cause physical barriers and disruption to the process of eating and swallowing. Neurological complications, from cancers which affect the nervous system pathways (often caused by compression of critical nerve pathways by tumour masses) may result in reduced or absent ability to swallow (*dysphagia*). Dysphagia may be complicated by ulcerous sores in the oral cavity (*stomatitis*) or through the gastrointestinal tract (*mucositis*).

Treatment of head and neck cancers directly impacts upon oral health, and upon swallowing ability. Surgical resections, with or without reconstruction, have direct impact upon oral functions, from full or partial removal of key anatomic areas associated with tumour masses. Radiotherapy, often given as adjuvant therapy following surgery, affects the tissues, with various effects depending upon anatomic structures within the radiated field.

The resultant inability to eat has significant consequences. Malnutrition and dehydration, from lack of intake of foods and fluids, directly and indirectly impact upon a patient's life. Reduced nutrients hamper many physiologic systems, and generally reduce a patient's quality of life and perfomance status. Patients with poor performance status have a generally poorer prognosis from cancer (and other diseases). Inability to eat also affects patients socially and emotionally. Eating is integral to life, and is a key part of our daily activities. Loss of eating ability removes the various pleasures we enjoy from eating, including our socialization with family and friends.

1.2. Oral Complications Induced by Cancer Treatment

Chemotherapy and radiotherapy can both have devastating effects on the oral cavity. The risk of oral complications is due to multiple factors. High turnover rates for cells lining the oral mucosa make this area susceptible to chemotherapy agents targeted to rapidly dividing cells. There is a diverse and complex natural microflora in the oral cavity, which can lead to opportunistic overgrowth by any of a large group of microbes. Normal responses of sensitive tissues, such as salivary gland dysfunction when exposed to radiotherapy, can become progressively worse with continued treatments. Trauma to oral tissues, which can occur during normal oral function, can exascerbate emergent problems from treatment toxicities. Also, anatomic and functional changes, resultant from cancers in the head and neck area, can further contribute to oral complications from the cancer therapies. Oral complications from chemotherapy and radiotherapy are listed in Tables 1 and 2.

Frequencies of oral complications from treatment may vary, depending on the type of therapy given; some frequency estimates include:

- 10% adjunctive chemotherapy for solid tumours (low risk)
- 40% primary chemotherapy (e.g. for hematologic malignancies) (intermediate risk)

- 80% hematopoietic stem cell transplant (HSCT) (high risk)
- 100% head and neck radiation therapy to fields involving the oral cavity.

The most common oral complications of cancer therapy include mucositis, infection (local or systemic), salivary gland dysfunction, taste alteration and pain, which result directly or indirectly, from the side effects of therapy. These complications can lead to secondary complications such as nutritional disorder, xerostomia or haemorrhage that may not be resolved with aggressive medical, nursing and dental interventions. As much as possible, oral complications should be prevented using good oral hygiene techniques.

The severity of these conditions may be affected by patient- and therapy-related variables. Examples of patient-related variables include the status of the patient condition before and during chemotherapy, and their compliance with treatments. Therapy-related variables include the type of chemotherapy agent(s) used, dosage, frequency of treatment, and the use of combination chemotherapy.

Understanding the circumstances in which oral complications can occur, and their clinical presentation enable healthcare professionals to implement interventions to prevent and resolve them. But oral side effects remain a major source of illness despite the use of a variety of approaches to prevent them.

In many cases, there is little clinical evidence of effect for the therapeutic interventions employed to alleviate specific problems in the mouth. It is common wisdom that the best strategy for mouth care is active prevention of potential problems. Although stringent prevention measures do not guarantee that complications will not occur, it is widely believed that the severity of oral complications will be less in those patients who exercise good oral hygiene. As well, there is some scientific rationale that strict adherence to oral hygiene measures may actually prevent clinical presentation of some oral complications. Thus, active health care teaching and reinforcement of mouth care procedures for patient self-administration is a key component of patient teaching in the health care institutions involved with cancer treatment.

1.3. Cost of Oral Complications

Oral complications associated with cancer therapy do not occur without a cost to the health care system. In a study of patients with head and neck cancer[1], 61% of patients treated with radiotherapy alone and 75% of patients treated with radiotherapy and chemotherapy developed grade 3/4 oral mucositis . These patients consumed ten-fold more nutritional services and supplies (TPN and tube feeds), and spent an additional 7 days in hospital, when compared with patients who had no mucositis (or 3 extra days for patients with low-grade mucositis). In this American centre, high-grade oral mucositis was associated with over $4,000 additional costs, above the baseline treatment costs. In another study of chemotherapy patients who experience myelosuppression, there were longer periods of hospitalization for those patients with oral mucositis compared with just neutropenia (6 vs. 4 days), and a higher rate of infection[2]. Oral mucositis is related to increased patient care costs in all risk groups.

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1. Elting LS. Oral mucositis: epidemiology and implications. Proc MASCC, 2006
2. Elting LS, Cooksley C, Chambers M, et al. The burdens of cancer therapy: clinical and economic outcomes of chemotherapy-induced mucositis. Cancer 2003; 98: 1531-9

Part 2. Anatomy and Pathophysiology of Oral Complications from Cancer and Cancer Treatment

2.1 Definitions

Dental Plaques: A combination of food, bacteria and bacteria by-products creating acidic waste that can lead to tooth decay

Denudation: The stripping or laying bare of any part

Dysgeusia: The presence of a chronic taste in the mouth (e.g. bitter, salty, metallic)

Lesion: An abnormal change in structure of an organ or part due to injury or disease

Leukoplakia: Well localized firmly attached white patches on the mucous membranes . Commonly considered precancerous

Mucositis: The pathologic effects of cancer treatments on the mucosal tissues lining the entire gastrointestinal tract

Non-keratinized: Tissue which does not include keratin

Plaque: A patch or flat area, sometimes a deposit of material

Pseudomembrane: A thick tough film on a mucous membrane, characterized as a false membrane

Stomatitis: The pathologic effects of cancer treatments on the mucosal tissues lining the oral cavity, as well as complicating sequelae from the therapies. Sometimes this is referred to as **Oral mucositis**, and often the terms are used interchangeably

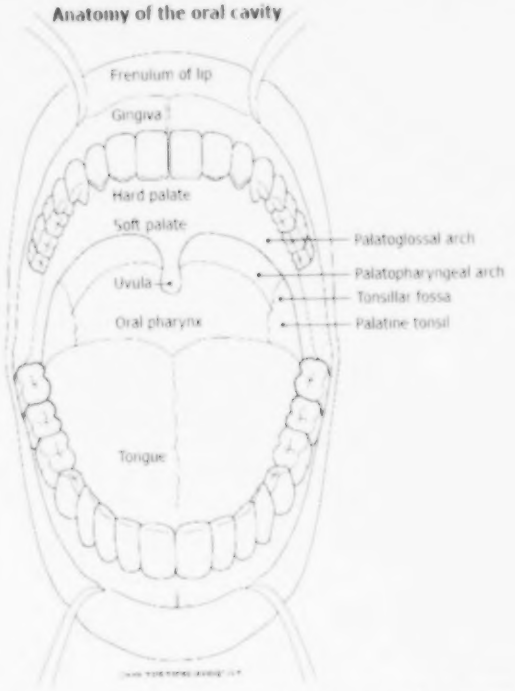
Stomatotoxicity: Refers more specifically to direct and indirect toxic effects of drugs and radiotherapy

Trismus: Spasm of the muscles of mastication resulting from any of various abnormal conditions or diseases

Ulcer: A break in skin or mucous membrane with loss of surface tissue, necrosis and sloughing of epithelial tissue, and often pus

Vesicle: A membranous and usually fluid-filled pouch (such as a cyst)

Figure 2.1



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Xerostomia: Abnormal dryness of the mouth due to insufficient secretions

2.2 Anatomy of the Oral Cavity

The oral cavity is composed of a mucosal lining of non-keratinized squamous epithelium composed of 15-20 layers of cells. These cells, and the underlying tissues, regenerate every 7-14 days. Salivary and sebaceous glands located beneath the surface of the epithelium lubricate the oral cavity.

Oral complications often result from epithelial and glandular destruction and inflammation. Because most treatment modalities destroy normal cells as well as cancer cells, normal tissues with high rates of proliferation (e.g., hair follicles, gastrointestinal tract, oral cavity) can be damaged by these toxic treatments.

2.3 Pathophysiology of Oral Mucositis

Oral complications following cancer therapies result from one of two mechanisms: a direct effect of the drug or radiation on the oral mucosa (direct stomatotoxicity) or an indirect result of myelosuppression from drug or radiation therapy (indirect stomatotoxicity). The clinical manifestations of direct and indirect stomatotoxicities are listed in Table III.b.

Direct stomatotoxicity results from the nonspecific effect on cells undergoing mitosis. It causes epithelial cells to cease replication, leading to mucosal atrophy and ulceration. Cell layers lost to abrasion during mastication are not replaced as quickly as they are lost.

Stomatitis may be seen 5-7 days after chemotherapy, and oral lesions often heal in about 2-3 weeks. This can be complicated by repeated cycles of chemotherapy. Radiotherapy to the oral cavity inevitably results in direct stomatotoxicity. Stomatitis may be further complicated by oral infections, which may exacerbate the mucositis and may progress to systemic infections.

Indirect stomatotoxicity is the result of the effects of chemotherapy (or radiotherapy of bone marrow) on the cells of the bone marrow, rather than the oral mucosa. Patients with hematologic malignancies or those who have received intensive radiotherapy and chemotherapy are most likely to become myelosuppressed. Reduced secretory IgA, a marker of immunosuppression, has been associated with stomatotoxicity. Infection and hemorrhage, worsened by neutropenia and thrombocytopenia respectively, are the two most common forms of indirect stomatotoxicity.

The risk of developing oral complications is affected by a variety of factors for each patient (e.g., type of malignancy, age, status of oral health before and during therapy), as well as for each treatment (e.g. chemotherapy agent(s), dosage(s), schedule, radiotherapy dose, duration). Patients treated for hematologic malignancies develop oral complications more often than patients treated for solid tumors, perhaps because these patients are functionally myelosuppressed as a consequence of their malignancies, but also due to more intensive chemotherapy regimens. Younger patients generally experience greater damage to the mucous membrane. Cell membranes replicate faster in younger people and these patients are at greater risk of mucositis.

Table 2.1 Oral Complications of Cancer Treatment [4]

Direct Toxicities	**Indirect Toxicities**
Oral mucositis	Myelosuppression
Salivary gland dysfunction	• Neutropenia
Neurotoxicity	• Immunosuppression
• Taste dysfunction	• Anemia
• Dentinal hypersensitivity	• Thrombocytopenia
Temporomandibular dysfunction	Infection
Dental & skeletal growth and development (pediatric patients)	• Viral (HSV, VZV, CMV, EBV, other)
	• Fungal (Candida, aspergillus, other)
	• Bacterial
	Graft-vs.-Host Disease (GVHD) after allograft
	Gastrointestinal mucositis
	Nausea and vomiting

Concomitant diseases (e.g., diabetes, AIDS, cardiopulmonary disease, kidney disease) may increase the risk. Treatment with other drugs may exacerbate xerostomia, including antidepressants, opiates, antihypertensives, diuretics, antihistamines, and sedatives.

Complications can be acute (developing during therapy) or chronic (developing months to years after therapy). For protocol purposes, one can classify acute effects as those appearing during therapy and up to day 90 from initiation of therapy; those that extend beyond day 90 or have their onset after that time can be classified as late effects or complications. In general, cancer chemotherapy causes acute toxicities that resolve following discontinuation of therapy and recovery of damaged tissues. In contrast, radiation protocols typically cause not only acute oral toxicities, but may induce permanent tissue damage that results in life-long complications for the patient.

2.2.1 Pathophysiologic and pathobiologic mechanisms

Although the exact pathophysiologic mechanism for mucositis is unknown, one hypothesis has been proposed from animal and clinical data.[6] Mucositis is proposed to be a complex process, which occurs in sequential phases (Table 2.2)

In the first phase, cytotoxic chemotherapy or radiotherapy causes the release of various cytokines, such as tumor necrosis factor-a, interleukin-1 (IL-1) and interleukin-6 (IL-6) from epithelial tissue and adjacent connective tissue. Cytokine release is the likely cause of local tissue damage, and subsequent inflammation. Increased amounts of IL-1 may also increase vascularity.

The second phase occurs a few days later. The direct cytotoxic effects of chemotherapy and radiotherapy (especially on the cell-cycle of renewal cells to maintain the tissue) result in reduced epithelial cell populations, and subsequent atrophy and ulceration. Locally produced cytokines and functional trauma (e.g. from mastication) contribute to the clinical symptoms at this phase. This phase also includes complex biologic changes in the submucosa, which may contribute more to the mucositis than direct cellular depletion.

The third phase is more complex than the first 2 phases. Local areas of erosion become coated with a fibrinous pseudomembrane. Coincidentally, this period often occurs when the patient reaches the nadir in neutrophil counts, and is at maximal risk of febrile neutropenia from infection. Secondary bacterial colonization of the oral mucosa, often involving gram-negative organisms, occurs. Some of the bacterial organisms produce endotoxins, which further stimulate cytokine release from surrounding connective tissue. In concert, the patient experiences maximal ulceration, infection and toxic response to released cytokines.

The fourth and final phase is healing. In this phase the epithelium renews itself through natural proliferation and differentiation of cell populations, in concert with normalization of circulating

Table 2.2 Pathophysiologic Phases in Development of Mucositis [5]

Phase 1	Inflammatory or vascular phase	day 0
Phase 2	Epithelial phase	days 4-5
Phase 3	Ulcerative or bacteriologic phase	days 6-12
Phase 4	Healing phase	days 12-16

white blood cells and the return of normal microbial flora to the oral cavity. This phase occurs about 2 weeks after the intial insult, but may be deferred if further insults are incurred (e.g. more radiotherapy or cycles of chemotherapy). As a rule, chemotherapy is held for 1-2 weeks in patients who experience significant stomatitis. This may not be the case for patients with imminently life-threatening cancers, such as acute leukemias.

The pathophysiologic model has more recently been expanded to include pathobiologic mechanisms. The complex pathobiology of mucosal barrier injury is currently understood by a model with five phases: initiation, upregulation with generation of messengers, signaling and amplification, ulceration with inflammation, and finally healing[7], as illustrated in Figure 2.2 It is evident that mucositis is more than just an epithelial event. This five-phase model also serves as a basis for understanding the rationale for therapeutic interventions as single agents or combination therapies.

Initiation

The primary event leading to mucositis is generation of oxidative stress and reactive oxygen species (ROS) by chemotherapeutic agents or radiation. ROS directly damage cells, tissues, and blood vessels. The activation of ROS and their subsequent stimulation of other transcription factors mark the initiation phase of mucositis and lead to other biologic events.

Up-regulation and generation of messenger signals

In the second phase, there are multiple simultaneous events. Clonogenic cell death in the epithelial layer results from DNA damage caused by ROS. The direct death of basal epthelial cells is not the only cause for clinical mucositis, however. Other biologic events are involved in the etiology of mucositis. Nuclear factor κB (NF-κB) is one transcription factor that is suspected to be a key element in the genesis of mucositis. NF-κB is activated by either radiotherapy or chemotherapy, and it has the capacity to upregulate several genes that can cause a range of tissue responses. Up-regulated genes are known to result in the production of the proinflammatory cytokines TNF-α, IL-1β, and IL-6 which leads to tissue injury and apoptosis. Expression of adhesion molecules, activation of the cyclooxgenase-2 pathway, and resulting angiogenesis is associated with upregulation of other genes.

There are other pathways of normal tissue apoptosis induced by chemotherapy or radiotherapy. Chemotherapy can activate the ceramide pathway, which may induce primary apoptosis. Fibronectin may break up during this phase of mucositis. Macrophages are then activated, causing matrix metalloproteinases to induce tissue injury directly or to produce TNF-α. The up-regulation and message-generation phase of mucositis involves tissue at all levels through several simultaneous events.

Signaling and amplification

Proinflammatory cytokines (TNF-α, IL-1β, and IL-6) are believed to not only cause direct damage to mucosal target cells but also to amplify radiation- and chemotherapy-induced mucosal injury indirectly. TNF-α activates pathways that can lead to tissue injury, such as the ceramide and caspase pathways and the transcription pathway mediated by NF-κB. These signals lead to further production of these proinflammatory cytokines. Activation of the ceramide pathway can be an effector mechanism for secondary TNF-α-mediated tissue

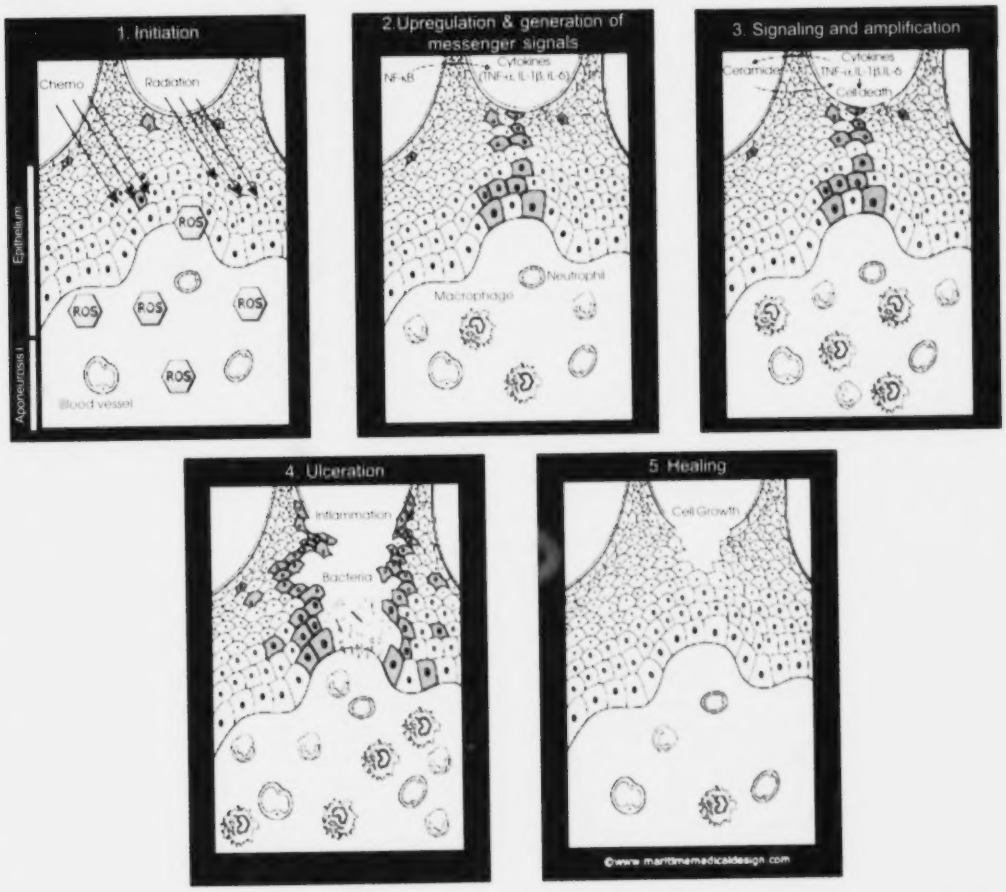
damage. This phase results in tissue that is biologically altered, even though it may appear normal.

Ulceration

Radiation-induced mucositis, and perhaps chemotherapy-induced mucositis, involves an inflammatory process. The significance of inflammation in mucosal barrier injury is uncertain, however. Since stomatitis occurs during the nadir of myeloablation in patients treated with chemotherapy, an acute inflammatory response would be minimal with reduced availablity of neutrophils. There is no histologic inflammatory infiltrate during the early stages of radiation-induced mucositis, but there is a robust infiltration of both round and polymorphonuclear inflammatory cells during the ulcerative phase.

Bacterial colonization with gram-positive, gram-negative, and anaerobic organisms occurs during the ulcerative phase. It is not clear how oral environmental factors such as bacteria and their products is related to mucositis. Bacterial cell wall products can activate tissue macrophages and increase production of the proinflammatory cytokines. Trials of bacterial load

Figure 2.2 **Pathophysiology of Oral Mucositis**



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reduction have shown erratic effect on the course of mucositis. Likewise, changes in the composition and amount of saliva may influence tissue susceptibility to cytotoxic agents and its ability to heal. Outcomes of mucositis studies are not clear on the impact of abnormal salivary function on mucositis. The consequences of ulceration are further cytokine amplification, inflammation, and pain. Regardless of whether bacteria are involved in the etiology of mucositis, the patient is at increased risk for bacteremia and sepsis.

Healing

The healing phase of oral mucositis starts with a signal from the extracellular matrix, leading to renewed epithelial proliferation and differentiation. The local microbial flora is re-established. Other associated clinical events, such as leucocyte recovery in stem cell transplantation patients, also return to normal. After the healing phase, the oral mucosa appears normal, but the mucosal environment has been significantly changed. Angiogenesis continues after healing appears completed. The patient is at increased risk of future oral mucositis episodes with further anticancer therapy.

Genetic risk and modulation of mucositis

Some aspects of mucositis risk are hypothesized to be genetically predetermined. Variations in susceptibility of individuals to chemotherapy-induced and radiotherapy-induced toxicities have long been observed. Single nucleotide polymorphisms that are associated with the metabolism of certain chemotherapeutic agents have been identified. Those individuals with a phenotypic deficiency of certain metabolic enzymes are less able to metabolize these chemotherapy drugs, and they are subsequently at greater risk for toxicity. There are other findings that suggest the risk of toxicity is determined in part by gender or ethnicity, but these require further study.

2.2.2 Radiation therapy

As radiation passes through a tissue, some of its energy is transferred to the cells causing ionization and producing highly reactive, although short-lived, free radicals within them. These, in turn, cause physical and chemical changes altering cellular structure and function(s) through interactions with deoxyribonucleic acid (DNA), ribonucleic acid (RNA) or intracellular enzymes causing faulty transcription, defective repair, metabolic disturbance, accelerated ageing and mutations. Since radiation cannot discriminate between normal and malignant cells both cell populations are vulnerable to damage. Its use in

Table 2.3 Oral Complications of Radiation Therapy [4]

Acute	**Chronic**
Oral mucositis	Mucosal fibrosis & atrophy
Infection	Xerostomia
• Fungal	Dental caries
• Bacterial	Soft tissue necrosis
• Viral	Osteoradionecrosis (ORN)
Salivary gland dysfunction	Taste dysfunction
• Sialadenitis	Dysgeusia
• Xerostomia	Ageusia
Taste dysfunction	Infections
Muscular/cutaneous fibrosis	• Fungal, bacterial

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eradication of tumour cells, therefore, depends on the differential sensitivity and recovery potential between tumor cells and normal tissues. [8-12]

The effects of irradiation on the oral cavity and oropharyngeal normal tissues (as listed in Table 2.3) depend on several factors, including:

- the type of radiation;
- the relative biologic efficiency (RBE) of radiation;
- the dose fraction;
- the time between fractions;
- the total irradiation dose (cumulative);
- the volume of the oral cavity which is irradiated (e.g. how much of the oral tissue is exposed to radiation);
- the introduction of rest periods during the treatment course;
- the overall treatment time (less effect on toxicities); and
- the anatomic structure(s) exposed to the stated dose.

With external irradiation, most or all the anatomic structures are at risk. The incidence of necrosis increases with irradiated volume and the magnitude of the dose.

Radiation therapy often causes extensive, permanent changes in salivary glands, bones, or oral musculature, which may lead to xerostomia, loss of taste sensation, infection, osteoradionecrosis, trismus, and extensive dental caries.[13]

The altered tissues are highly susceptible to infection, especially fungal organisms such as Candida albicans or other Candida subspecies. Bacterial and viral infections may also occur.

2.2.3 Chemotherapy

Antineoplastic (cytotoxic) drugs play a dual role in cancer therapy both as the primary treatment of choice for many widely disseminated malignancies or as an adjunct to surgery or radiotherapy. Treatment of cancer with chemotherapy is becoming increasingly more effective but, like radiotherapy, is associated with short and long-term side effects. [12,14-7] Common chemotherapy agents associated with mucositis are listed in Table 2.4.

Cancer chemotherapy agents are used in treatment to destroy, suppress, or prevent the spread of malignant cells, which have a high proliferative rate. Because chemotherapeutic agents are not specifically targeted against cancer cells, they also adversely affect normal host cells that have a high mitotic index. Normal cells that are susceptible to this adverse affect include those of the oral and gastrointestinal (GI) mucosa, hair follicles, the reproductive system, and the hemopoietic system.

Table 2.4 Cancer Chemotherapy Agents Which Cause Mucositis [5,18]

Amsacrine	Docetaxel	Mechlorethamine
Bleomycin	**Doxorubicin**	Mercaptopurine
Busulfan	**Epirubicin**	**Methotrexate**
Carboplatin	**Etoposide**	**Mitoxantrone**
Chlorambucil	**5-Fluorouracil**	Mitomycin
Cisplatin	Fludarabine	Paclitaxel
Cyclophosphamide	Gemcitabine	Procarbazine
Cytarabine	**Idarubicin**	**Vinblastine**
Dacarbazine	Irinotecan	Vincristine
Dactinomycin	Hydroxyurea	Vinorelbine
Daunorubicin	Lomustine	

Note: Agents in **bold print** have higher likelihood of mucositis

Table 2.5 Oral Complications of Cancer Chemotherapy [18]		
Complication	**Direct Risk Factor**	**Indirect Risk Factors**
Oral mucositis	Mucosal cytotoxicity Physical/chemical trauma Re-activation of HSV	Decreased local/systemic immunity local infections
Oral infections		
• Viral		Decreased systemic immunity
• Fungal		Decreased systemic immunity Salivary gland dysfunction Altered oral flora (decreased bacterial flora)
• Bacterial	Inadequate oral hygiene Mucosal breakdown Acquired pathogens	Decreased systemic immunity Salivary gland dysfunction
Taste dysfunction	Taste receptor toxicity	
Xerostomia	Salivary gland toxicity	Anticholinergic drugs
Neuropathies	Vinca alkaloid drug use	
Gastrointestinal mucositis		Nausea and vomiting
Hemorrhage	Oral mucositis	Thrombocytopenia

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Many chemotherapeutic agents exert direct destructive effects on tissues in or around the oral cavity. The agents may also act indirectly by inducing myelosuppression and/or immunosuppression. Frequency and severity of oral complications are directly related to extent and type of systemic compromise. Complications are often compounded by simultaneous or sequential administration of mixtures of chemotherapy drugs. Although these factors are taken into account when planning individual treatment, it should be recognized that there is often only a narrow margin of safety between tumoricidal and toxic doses. Because the aim of therapy is to maximize destruction of malignant cells, the risk of at least some toxicity should be accepted. By combining agents with different mechanisms of action and different dose-limiting toxicities, it is possible to optimize the doses of individual drugs for maximum anti-tumour activity. Such combinations, although they may enhance the response to therapy, may increase the range and severity of side effects, particularly those which are not the dose limiting toxicities of the individual drugs.

Although oral tissue responses to chemotherapy show considerable individual variation, their manifestations are usually related to the total dose and the drugs received. Patients who develop oral toxicity during initial therapy are likely to continue to exhibit toxic symptoms throughout treatment, unless changes are made to the planned regimen. Combination drug therapy or chemoradiation therapy is more likely to induce longer-lasting lesions.

Affected oral soft tissues are exposed to physical, chemical, thermal, and microbial injury. The oral cavity may become the focus of chemotherapeutic complications, especially if there is

concurrent bone marrow suppression. Oral complications from chemotherapy are similar to those induced by radiation, although sometimes more transient in nature.

Xerostomia, dysphagia, and dysgueusia are common problems, and are more likely in patients with mucositis, soft tissue ulceration, or oral infection. Mucositis may be quite severe, with onset occurring

Table 2.6 Oral Complications of Hematopoietic Stem Cell Transplantation[19]

Transplant Phase	Oral Complication
Phase I: Preconditioning	Oral infections: dental caries, endodontic infections, periodontal disease (gingivitis, periodontitis), mucosal infections (i.e., viral, fungal, bacterial). Gingival leukemic infiltrates. Metastatic cancer. Oral bleeding. Oral ulceration: aphthous ulcers, erythema multiforme. Temporomandibular dysfunction.
Phase II: Conditioning Neutropenic Phase	Oropharyngeal mucositis. Oral infections: mucosal infections, periodontal infections. Pain in the mouth and/or lips. Reduced ability to eat, drink and talk. Reduced ability to perform oral hygiene. Hemorrhage. Xerostomia. Taste dysfunction. Neurotoxicity: dental pain, muscle tremor (e.g., jaws, tongue). Temporomandibular dysfunction: jaw pain, headache, joint pain.
Phase III: Engraftment Hematopoietic Recovery	Oral infections: mucosal infections. Acute graft-versus-host-disease (GVHD). Pain in the mouth and/or lips. Reduced ability to eat, drink and talk. Reduced ability to perform oral hygiene. Xerostomia. Hemorrhage. Neurotoxicity: dental pain, muscle tremor (e.g., jaws, tongue). Temporomandibular dysfunction: jaw pain, headache, joint pain. Granulomas/papillomas.
Phase IV: Immune Reconstitution Late Post-transplant	Oral infections: mucosal infections. Chronic GVHD. Dental/skeletal growth and development alterations (pediatric patients). Pain in the mouth and/or lips. Xerostomia. Relapse-related oral lesions. Second malignancies.
Phase V: Long-term Survival	Ongoing chronic GVHD of the lips and mouth. Pain in the mouth and/or lips. Relapse or second malignancies. Dental/skeletal growth and development alterations.

May be duplicated for use in clinical practice. As appears in: Broadfield L, Hamilton J. Best Practice Guidelines for the Management of Oral Complications from Cancer Therapy. © *Cancer Care Nova Scotia*, 2006

within 7 days of initiation of chemotherapy and duration varying from several days to weeks. Gingival bleeding is found during nadir periods of maximum myelosuppression.

Chemotherapy may also cause salivary changes and sensory neuropathies. Many cytotoxic drugs will cause a degree of myelosuppression secondary to therapy. This usually occurs 7 to 14 days after treatment. The resultant neutropenia and thrombocytopenia will place the patient at increased risk from infection and hemorrhage.

2.2.4 Hematopoietic Stem Cell Transplantation (HSCT)

Patients undergoing hematopoietic stem cell transplantation experience more profound and severe oral complications than those receiving less intensive doses of chemotherapy and/or radiotherapy. Conditioning regimens to partially or fully ablate the hematopoietic tissues have been reduced in myelotoxic intensity in more recent years, but these regimens are not necessarily less stomatotoxic. Oral complications may change through the phases of HSCT, as noted in Table 2.6.

Phase I: Preconditioning for HSCT

Before conditioning chemotherapy, oral complications are secondary to the underlying disease, and prior treatments for cancer (e.g. chemotherapy) or other medical conditions. Pre-treatment problems with oral health including dental caries, periodontal disease, and pulpal infection, should be addressed and resolved (if possible). At this phase, dental screening should be performed and patient education should begin, including information about potential oral complications, methods to manage the symptoms, and basic oral hygiene.

Phase II: Conditioning Neutropenic Phase

This phase is usually the period during which oral complications are most common and most severe. Oral complications are associated with high-dose chemotherapy or chemoradiotherapy. Mucositis, xerostomia, and lesions related to myelosuppression, thrombocytopenia, and anemia predominate.

Oral mucositis usually begins 7 to 10 days after cytotoxic chemotherapy or chemoradiotherapy, and continues for approximately 2 weeks. Viral, fungal, and bacterial infections may occur during this time of greatest risk. Infections are dependent on oral status prior to chemotherapy, and duration/severity of neutropenia. Infections decline when mucositis is resolved and neutrophil counts return to normal. Patients who have poor immune system reconstitution may remain at risk, however.

Xerostomia and taste dysfunction may begin in this phase. These toxicities typically resolve within 2 to 3 months.

Phase III: Hematopoietic Recovery

Acute oral complications begin to resolve 2 to 4 weeks after the conditioning regimen. As the bone marrow regenerates, ulcerative oral mucositis will begin to heal. Immune defenses in the oral mucosa will still take time to return to normal and patients remain at risk for certain types of infection, including candida and herpes simplex virus. Bacterial infections of the oral mucosa are less common during this phase, except in patients for whom engraftment is delayed, patients with acute graft-versus-host disease (GVHD- more common in allogeneic transplant patients), or patients receiving GVHD therapy.

Phase IV: Immune Reconstitution/ Recovery from Systemic Toxicity

Oral complications are among the chronic toxicities experienced by many hematopoietic stem cell transplant patients. Late viral infections and xerostomia are most common, and bacterial infections are infrequent. The hematopoietic stem cell transplant patient may develop oral manifestations of chronic GVHD during this period.

Phase V: Long-term Survival

There are few significant oral complications in long-term survivors of HSCT. Allogeneic transplant patients may experience severe oral symptoms from ongoing chronic GVHD of the lips and mouth.

Patients treated with high-dose radiotherapy (such as total body irradiation- TBI) may have oral complications associated with the total dose and schedule of radiation therapy. Xerostomia is the most common long-term oral complication from Total Body Irradiation.

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Part 3. Assessment of Oral Complications from Cancer Therapy

3.1 Dental assessment

Dental assessment and interventions should be arranged prior to the start of chemotherapy or radiotherapy. See Part 4 for details about dental care of the oncology patient.

3.2 Screening for oral complications

Best Practice Statement:

*Ambulatory patients and hospital inpatients on chemotherapy should be **screened** on a regular basis with the Stomatitis Staging System scale for evidence of oral complications. Inspection of the oral cavity using a flashlight should be included in the systematic screening of patients at each visit during chemotherapy treatment (or daily for inpatients on chemotherapy).*

*If stomatitis or other oral complications are identified and become a focus of care, routine **assessment** should begin (see Part 3.3).*

*Patients at high risk of serious oral complications (e.g. HSCT patients, or patients receiving radiotherapy to the oral cavity area) should not be screened, but should begin with routine **assessment** (see Part 3.3) in anticipation of oral complications.*

Since the risk of oral complications during active treatment with chemotherapy is not predictable, a regular screening process should be included with ongoing assessment of patients. Visual inspection of the oral cavity and discussion of possible symptoms with the patient are necessary to properly assess the patient for emerging oral complications.

The only validated tool for screening of oral complications is the *Stomatitis Staging System*- Table 3.1 (previously referred to as the WCCNR Stomatitis Staging System- see below). Historically, common practice had been to screen for stomatitis using the NCI Common Toxicity Criteria, which has never been established as a reliable and valid tool. The Stomatitis Staging System (SSS) is a simple, validated tool based on objective observation by a health care professional. Using a flashlight to examine the oral cavity, the oral mucosa is rated for the number of visible lesions, the tissue colour (erythema), and the amount of bleeding observed. The scores for each criterion are added together and the sum is categorized as Normal, Mild, Intermediate, or Severe Stomatitis. Patients may be screened prior to the start of each chemotherapy cycle, or weekly during radiotherapy treatments, to identify emerging problems with oral complications.

Patients who are receiving treatment in hospital should be screened daily with the Stomatitis Staging System and documented in the progress notes or patient care flow sheet. If stomatitis or other complications develop, switch from screening to a routine assessment using the Mouth Care Record (MCR) for documentation. When symptoms resolve, return to routine screening as above. Current therapy may need to be altered if oral complications are identified or are becoming worse.

3.3 Oral assessment

Best Practice Statement:

*When stomatitis or other oral complications are identified from screening and become a **focus of care**, **routine assessment** should begin. For high-risk patients, **routine assessment** should begin at the start of treatment.*

Assessment includes rating mucositis (using the Stomatitis Staging System scale), and considers a range of oral symptoms and response(s) to interventions over time. The MCR will be

Table 3.1 WCCNR STOMATITIS STAGING SYSTEM [17]			
Add the scores of the lesions, colour and bleeding to identify the stomatitis stage: 0 = **N**ormal; 1-4 = **M**ild; 5-7 = **I**ntermediate; 8-9 = **S**evere			
SCORE	**LESIONS**	**ERYTHEMA (COLOUR)**	**BLEEDING**
0	None	More than 50% pink	None
1	1-4	More than 50% slightly red	None
2	More than 4	More than 50% moderately red	Bleeding with eating or mouth care
3	50% or more denuded	More than 50% very red	Spontaneous

Note: Denuded refers to the surface layer removed, and lesions spreading together or coalescing. Reproduced with permission- ©2004 Olsen et al.

used for documentation of routine assessment until the oral complications are resolved.

Assessment should be incorporated into both the Basic and Intensified Mouth Care Plans.

3.3.1 Development of oral assessment tools

Oral screening should take place at the first meeting with the patient[1] because evidence suggests that screening prior to cancer treatment can reduce both the incidence and severity of oral complications for the patient.[2] Oral assessment tends to be very subjective, so valid comparisons of the oral cavity's actual state require the use of a well-tested and validated tool.[3] There are many assessment tools in use today to systematically assess the oral cavity. Most of these tools were adapted from tools developed in the 1960's and early 1970's, when instruments were being developed to assess degrees of stomatitis and the effects of interventions for the patient with mouth problems. Many instruments developed for research purposes have been adapted for use in day-to-day practice. In cancer care, established centres use systemic mouth care assessment instruments as a guide for assessment and documentation.

In 1960, Greene and Vermillion developed a numerical rating guide as a method for classifying oral hygiene status[4]. In 1966, Passos and Brand did further work with Greene and Vermillion's guide to evaluate the effectiveness of three oral care agents.[5] Eight categories (saliva, tongue, palates, membranes/gums, teeth, odor, lips and nares) were given a rating from 1-normal to 3-severe, which were added together to achieve a total score. There is no report of psychometric testing.

Vandrimmelsen and Rollins adapted Passos and Brand's 8-item tool and created an 11 item scale to examine the effectiveness of lemon juice and glycerine as an oral agent.[6] The investigators tried to increase reliability of conducting the assessments, but there was no evidence that the assessment tool itself went through any psychometric testing.

Dewalt published results from work conducted using an adapted version of Passos and Brand's numerical rating guide.[7] Dewalt's work included how the assessment was to be done and how it was to be measured. Inter-rater reliability was measured.

In 1975, Bruya and Madeira developed an assessment tool for assessing stomatitis

after the administration of chemotherapy.[8] They used the previous work of Dewalt, Passos and Brant, VanDrimmelsen and Rollins, to build their 17-item scale. The 17 items included level of consciousness; breathing habits; nutritional status; chewing ability; self-care ability; the texture, colour and moisture of the lips and tongue; mucous membranes, gingival tissue, teeth, saliva, taste and voice. Items were rated between 1 and 3. No psychometric tested was evident, however, it became foundation work for future studies because of the extensive review of normal and abnormal oral cavities.

Beck developed three assessment tools – the oral examination guide – for use in her descriptive study to determine if teaching nursing staff about stomatitis and an oral care protocol improved oral exam scores of patients receiving chemotherapy.[9] Baseline evaluation was conducted. The tools consisted of:

1) An "Oral Exam Guide", a combination and adaption of previously identified tools from a variety of disciplines. Sixteen descriptions were identified to numerically rate the condition of the patient's mouth.
2) An Oral Perception Guide, in which the nurse rated the patient's sensory perception of the mouth, teeth, taste, voice changes, and abililty to eat.
3) Physical Condition Tool, which rated the patient's general physical condition (self-care ability, diet, breathing habits and level of consciousness).

Each category was numerically scored between 1 and 4. Because Beck collected all of the data herself, variability due to more than one rater was eliminated, otherwise, no psychometric testing was evident.

In the late 1970's and early 1980's, the term "grading system" was beginning to be used in the descriptions of mouthcare and in assessing stomatitis severity with cancer therapy.

A well-known oral assessment guide is the Eiler's oral assessment guide (OAG).[10] Many assessment tools currently used in practice today are based on Eiler's OAG. Eight items (lips, tongue, mucous membranes, ginvia, teeth/dentures, voice, swallow, saliva) are rated on a 1-3 scale. Some reliability and validity testing was conducted. Users found the tool clinically useful.

The MacDibbs Mouth Assessment was specifically developed for use with patients with stomatitis due to radiotherapy.[11] Along with items in a physical examination, patients rate their pain, dryness, eating, talking, swallowing, tasting and saliva production on a scale from 0 to 3. A smear and culture are done to check for fungal and viral infection. There are 14 items in total to be examined. Scoring is not well defined. Content validity was established by a panel of experts. Unlike other tools, the MacDibbs Mouth Assessment is able to distinguish between radiotherapy-induced stomatitis and infection.

Difficulties have been identified with tools that have numerous items that need to be evaluated. These tools can be time consuming for the health provider and the patient. With a number of items, the same score can be obtained in a variety of ways, so that two different people can have different severities of stomatitis. As well, if items are not specific or detailed enough, the tool will not distinguish between stomatitis and other oral health problems.

In 1981, the World Health Organization (WHO) held two meetings with

representatives from the largely recognized cancer organizations (the European Organization for Research on Treatment of Cancer, The National Cancer Institute, and The International Union Against Cancer). The outcome of these meetings was the WHO grading toxicity scales.[12] The grading system ranged from 0 (no side effects) to 4 (unable to eat or drink). A standardized assessment and reporting method for mucositis became recognized and used globally. No evidence of biometric or psychometric testing for this tool was found. It is used by many groups conducting co-operative clinical trials. Despite the popularity of this grading system, there is criticism that the descriptors at each level are not specific enough. Level 4 (unable to eat or drink), for example, does not establish if the patient is not able to eat or drink because of the stomatitis or because of another reason.

Scores from the expanded common toxicity scale, developed by the National Cancer Institute of Canada Clinical Trials Group, were compared with scores of the WHO grading toxicity scale by Brundage et al.[13] With poor levels of agreement, the investigators concluded that varying conclusions could be drawn from the assessor, and that neither scale demonstrated clear superiority. The Common Toxicity Criteria, used by the NCIC, has further evolved to be included in the CTEP Common Toxicity Criteria for Adverse Events (CTCAE).[14] Neither have been tested for reliability or validity, yet these have been adopted as the "gold standard" for assessment and evaluation in clinical trials.

The Western Consortium for Cancer Nursing Research (WCCNR) was interested in developing a tool for clinical use with patients receiving cancer treatment.[15] In the first phase of the tool development, descriptors that were valid indicators of stomatitis severity were identified. Each of 4 stages had descriptors related to mucosal color, lesions, bleeding, moisture, edema, infection, ability to eat/drink, and discomfort. Testing was done on patients with chemotherapy-induced stomatitis along with the Eiler's Oral Assessment Guide[10] and the WHO Grading system.[12] Correlation with these tools was 0.76 and 0.69 respectively. Discriminant analysis of the results revealed that using all 8 predictors, 98% of patients were correctly staged. 96.4% of patients were correctly staged when using only the descriptors of color, lesions and bleeding. In further study[16], the 3 item staging system (the Stomatitis Staging System, or SSS) was evaluated to establish reliability and concurrent validity in patients receiving chemotherapy, radiation therapy and a combined chemotherapy and radiation therapy. The MacDibbs Mouth Assessment[11] was used to establish validity with the radiation therapy patients. Two hundred and thirty patients were staged. Results indicated that the WCCNR SSS tool is a reliable and valid tool for assessing stomatitis severity with these three populations of patients.

The WCCNR SSS tool is the only tool for mouth assessment with validity and reliability data for radiotherapy, chemotherapy and combination therapy[17], and is recommended in this guideline as the tool of choice for assessing the mouth through treatment. The Mouth Care Record incorporates the WCCNR stomatitis scales to ensure consistency between screening and assessment of oral complications.

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Table 3.2

Mouth Care Record for Cancer Patients

Dental Assessment: Date Completed_____

STOMATITIS STAGING SYSTEM

Add the scores of the lesions, colour and bleeding to identify the stomatitis stage 0 = **N**ormal; 1-4 = **M**ild; 5-7 = **I**ntermediate; 8-9 = **S**evere

SCORE	LESIONS	ERYTHEMA (COLOUR)	BLEEDING
0	None	More than 50% pink	None
1	1-4	More than 50% slightly red	None
2	More than 4	More than 50% moderately red	Bleeding with eating or mouth care
3	50% or more denuded	More than 50% very red	Spontaneous

MOUTH ASSESSMENT		DATE:												
		TIME:												
Stomatitis see Stomatitis Staging System above	Lesions													
	Colour													
	Bleeding													
	Total Score													
	Stomatitis Stage (N, M, I or S)													
Pain (0-10 scale)	Mouth Pain													
	Throat Pain													
	Pain on Swallowing													
Function (**Y**es or **N**o)	Xerostomia													
	Taste Altered													
	Able to swallow													
Eating Check (✓)	Eating all foods													
	Liquids only													
	Not eating or drinking													
Suspected Infection (**Y** or **N**)														

MOUTH CARE PLAN

Care Plan Check (✓)	Basic												
	Intensified												
Stomatitis & Pain Check (✓)	Coating Agent												
	Lubricant												
	Pain Medication Needed (**Y** or **N**)												
	Topical Analgesic (ie. Benzydamine)												
	Anesthetic/Pain Relief Mouthwash												
	Systemic Analgesic												
HSCT/BMT Patients	Parenteral (IV) Opioid												
	Somnolence Score (1-4)												
Infection Management (**Y** or **N**) Check (✓)	Systemic Antifungal(s)												
	Topical Antifungal(s)												
	Other Antibiotic(s)												
Care Provider Check (✓)	Self												
	Assisted												
	Totally by Other												
Patient Teaching- Check (✓)													
Notes- (✓)													
Initials													

3.3.2 The Mouth Care Record for Cancer Patients

The **Mouth Care Record for Cancer Patients** (MCR- Table 3.2) is a tool developed for systematic assessment and documentation of oral complications when this has become a focus of care. Patients at high risk for oral complications will begin with assessment using the MCR from the start of cancer treatment.

The MCR form includes areas to rate and document stomatitis, mouth pain, function, ability to eat, and presence of suspected infection. The MCR also simplifies documentation of oral care interventions (including the mouth care plan). If oral pain is a focus of care, use the pain assessment section of the MCR for ongoing assessment. If pain is more complicated than just the mouth, then use the standard pain assessment tools (see Guidelines for the Management of Cancer-Related Pain) concurrently with the MCR. If infection is a focus of care, assessment and management would be documented as per usual practice in the health record.

The frequency of oral assessment, and the tools to use, are outlined in Table 3.3.

Table 3.3 - Frequency and Tool Selection for Oral Screening and Assessment

	Low Risk (10-40%) Adjuvant/Palliative Chemotherapy for most Solid Tumours	**Intermediate Risk** (40%) Chemotherapy for Hematologic Malignancies, some Gastrointestinal Cancers	**High Risk** (80%) Hematopoietic Stem Cell Transplant AND (100%)-Radiotherapy for Head & Neck Cancers
Screening Through Treatment	**Ambulatory Patients:** Rate with SSS at each visit **Inpatients:** Rate with SSS once daily **Documentation:** On nursing flow sheet and/or progress notes	**Ambulatory Patients:** Rate with SSS at each visit **Inpatients:** Rate with SSS once daily each morning **Documentation:** On nursing flow sheet and/or progress notes	**Ambulatory Patients:** Conduct assessment at each visit **Inpatients:** Conduct assessment at least once each shift **Documentation:** On Mouth Care Record (MCR)
Assessment when oral complications become a focus of care	**Ambulatory Patients:** Assess all symptoms at each visit until resolved, then return to screening **Inpatients:** Assess all symptoms at the start of each shift **Documentation:** On Mouth Care Record (MCR)	**Ambulatory Patients:** Assess all symptoms at each visit until resolved, then return to screening **Inpatients:** Assess all symptoms at least once in each shift **Documentation:** On Mouth Care Record (MCR)	**Ambulatory Patients:** Assess all symptoms at each visit until resolved, then return to screening **Inpatients:** Assess all symptoms at least twice during the day shift and once during the night shift **Documentation:** On Mouth Care Record (MCR)

3.4 Ongoing Assessment of Patients When Oral Complications Are Resolved

When oral complications have resolved, ongoing assessment may cease and the patient may continue to be screened with CTC at follow up visits or once daily in hospital. Some HSCT patients may require long-term screening, due to chronic oral complications from graft-versus-host disease or other long term effects.

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Part 4. Dental Assessment and Care of the Cancer Patient

4.1 Dental Assessment

Best Practice Statement:

Patients who are scheduled to receive chemotherapy of any kind should be assessed by a dentist prior to the cancer treatment. Patients who will receive radiotherapy to the head and neck, or hematopoietic stem cell transplant must be assessed by a dentist prior to treatment. For these patients at high risk for oral complications, the dental assessment should be done by a dental team experienced with oral oncology. Other dental assessments may be done by the patient's community dentist in consultation with the oncology specialist(s). The dental examination and assessment should be done as soon as possible, to allow time for any dental procedures and adequate healing prior to the cancer treatment. If dental work is indicated, this should be carried out before cancer treatrment is started. Dental exams may be repeated during active therapy on the advice of the oncology team.

Prior to the start of chemotherapy or radiotherapy, it is advisable for patients to visit their dentist (or oncology dental specialist, where available) for a thorough physical inspection of the oral cavity, and dentition. If there are pre-existing problems with oral health, these should be considered for rapid resolution, if possible[8].

Patients scheduled to receive radiotherapy to the head and neck require dental assessment (and, when indicated, a maxillofacial prosthodontic examination) before radiotherapy, to address factors which can predispose the patient to osteoradionecrosis (ORN- section 5.19) and other radiation-induced

Table 4.1 Communications with Dental Oncology Team

Pre-treatment Dental Exam

The dentist should receive key information about the cancer patient prior to the assessment, including:

- Cancer diagnosis, such as type, stage, prognosis
- Current CBC and other relevant bloodwork results; hematologic and immunologic status
- Treatment planned for the patient, including planned date for first treatment
- If radiation is planned, field and dose of radiation
- If the patient is to receive a stem cell transplant, type of transplant, planned transplant date, conditioning regimen to be given
- Other medical considerations, such as splenectomy, cardiopulmonary disease, indwelling venous access line

Assess as early as possible- one month before cancer treatment if invasive oral procedure(s) needed

Information to Send Back to Oncology Team:

- Amount & severity of dental caries
- Number of teeth requiring restoration or extraction
- Teeth requiring endodontic treatment, or other endodontic disease issues
- Periodontal disease status
- Teeth with pupal infection
- Any other urgent dental care required
- Time needed to stabilize any oral disease

oral toxicities. A dental team experienced with oral oncology may reduce the risk of oral complications through direct examination and interventions for the cancer patient prior to cancer therapy, especially treatments with intermediate to high risk of stomatotoxicity. The oncology dental team, or the oncologist may also work in consultation with the patient's community-based dentist. The oncologist or oral oncology team should be in contact with the community dentist, to determine how best to schedule an assessment and any necessary dental work in context of the planned cancer therapy. In some circumstances, the dental assessment and subsequent intervention(s) may be done by the hospital dental team. Patients scheduled for a hematopoietic stem cell transplant procedure should also be referred for a pre-treatment dental assessment by the oncology dental team.

The assessment and resolution of any pre-existing dental problems should occur as early as possible prior to treatment.[1-3] The dental examination allows the dentist to initiate necessary interventions that may reduce oral complications during and after the cancer therapy. The examination should be performed at least 1 month prior to cancer treatment to permit adequate healing from any invasive procedures.

To facilitate the dental assessment, the oncology team or oncologist should provide relevant information to the dentist[3], as listed in Table 2.1. At the dental assessment visit, an oral hygiene program for the duration of the cancer therapy should be started. The dental team should communicate back to the oncology team on the dental assessment and interventions conducted. The dental team may also develop a care plan for oral disease management before, during, and after cancer therapy.

If not consulted before hospital admission, the Capital Health Department of Oral and Maxillofacial Surgery may be consulted for patients treated in the CDHA district; for other districts patients may speak with their oncology specialists for local consultation options.

When chemotherapy is planned, particularly for hematologic malignancies, the patient may be referred for dental consult before treatment, and dental care may be provided by the patient's own dentist either before or after cancer treatment.

4.2 Dental Management Before Chemotherapy and/or Radiotherapy

Upon completion of a thorough dental assessment, the dental team may opt to perform appropriate and necessary procedures, to establish optimal oral health prior to cancer treatment (see Figure 4.1). The community dentist may opt to refer the patient to an oral surgeon or oral pathologist for certain procedures. Specific dental interventions prior to cancer treatment may be directed to (as necessary):

- Mucosal lesions
- Dental caries and endodontic disease
- Periodontal disease
- Ill-fitting dentures
- Orthodontic appliances
- Temporomandibular dysfunction
- Salivary abnormalities

Guidelines for dental extractions, endodontic management, and related interventions can be utilized as appropriate.[4,5] Antibiotic prophylaxis prior to invasive oral procedures may be needed, particularly if the patient is neutropenic. The following guidelines may help the dental team to determine the need for antibiotics or transfusions in

Figure 4.1 Dental Assessment & Interventions for Cancer Patients

LOW RISK (10%)
Adjuvant/Palliative Chemotherapy Patients

Pre-treatment Dental Exam

The dentist should receive key information about the cancer patient prior to the assessment, including:

- Cancer diagnosis, such as type, stage, prognosis
- Current CBC and other relevant bloodwork results; hematologic and immunologic status
- Treatment planned for the patient, including planned date for first treamtent
- If radiation is planned, field and dose of radiation

Assess as early as possible- one month before cancer treatment if invasive oral procedure(s) needed

Pre-treatment Interventions

May be directed to (as necessary):

- Mucosal lesions
- Dental caries and endodontic disease
- Periodontal disease
- Poorly-fitting dentures, orthodontic appliances
- Temporomandibular dysfunction
- Salivary abnormalities
- Patient education on oral hygiene plan

By community dentist or on referral to oral surgeon or oral pathologist

Information to Send Back to Oncology Team:

- Amount & severity of dental caries
- Number of teeth requiring restoration or extraction
- Teeth requiring endodontic treatment, or other endodontic disease issues (or recommendation for chlorhexidine use)
- Periodontal disease status
- Any other urgent dental care required
- Time needed to stabilize any oral disease

Post Chemotherapy:

- Avoid dental work during periods of chemotherapy-induced neutropenia and/or thrombocytopenia
- Regular dentist and dental hygienist visits (annual or more often as needed) after chemotherapy is complete
- Watch for evidence of osteonecrosis of the jaw (ONJ) in patients given injectable bisphosphonates e.g. Pamidronate, Zoledronic Acid; if there is evidence of risk of ONJ, avoid dental extractions and consider concomitant topical and systemic antiobiotics.

INTERMEDIATE RISK (40%)
Primary Chemotherapy (e.g. Hematologic Malignancy) & some Gastrointestinal Cancer Chemotherapy Patients

Same as Low Risk, plus

- Pre-treatment dental exam and interventions may be performed by oral oncology team/hospital dentist or referred to community dentist

Post Chemotherapy:

- Same as Low Risk

May be duplicated for use in clinical practice. As appears in: Broadfield L, Hamilton J. Best Practice Guidelines for the Management of Oral Complications from Cancer Therapy. © *Cancer Care Nova Scotia*. 2006

Figure 4.1 Dental Assessment & Interventions for Cancer Patients (continued)

HIGH RISK (80-100%)
Head & Neck Cancer Patients on Radiotherapy

Same as Low Risk, plus
- Comprehensive pre-treatment dental exam and interventions may be performed by oral oncology team/hospital dentist or referred to community dentist, oral surgeon or oral pathologist
- Fabrication of custom flouride trays or PrevDent for radiation patients
- Pre-treatment assessment by prosthodontist prior to any radiotherapy to the head and neck; preparation and fitting for prosthodontic appliances as required
- Eliminate oral disease before treatment (e.g. dental extraction of high-risk dentition) for radiotherapy patients

Post Radiotherapy:
- Annual follow-up visits with prosthodontist and regular visits to dentist (every 4 months) for cleaning and assessment (dental caries prevention)- for 2 years after radiotherapy.
- Then annual dentist visits (or more often as needed)
- Daily oral fluoride tablets (e.g. Prevident) may be used to avoid ongoing superficial fluoride applications.

HIGH RISK (80-100%)
Bone Marrow/Stem Cell Transplant Patients

Same as Low Risk, plus
- Comprehensive pre-treatment dental exam and interventions may be performed by oral oncology team/hospital dentist or referred to community dentist, oral surgeon or oral pathologist
- Eliminate oral disease before treatment (e.g. dental extraction of high-risk dentition)

Post Transplant:
- Caution with any oral treatments or interventions (including dental scaling & polishing) for at least one year after transplant, even if hematology parameters return to normal and graft-versus-host disease has resolved; patient immune systems do not return to normal for at least one year post-transplant

May be duplicated for use in clinical practice. As appears in: Broadfield L, Hamilton J. Best Practice Guidelines for the Management of Oral Complications from Cancer Therapy. © *Cancer Care Nova Scotia*, 2006

the cancer patient population (adapted from the American Heart Association (AHA) protocol for infective endocarditis and oral procedures[6,7]):

- Patients with chronic indwelling venous access lines (e.g., Hickman). - Consider empiric prophylactic antibiotics (low risk).
- Neutrophils 1.0-2.0 x 10^9/L - Consider empiric prophylactic antibiotics (low risk).
  - Amoxicillin 2 g PO given 1 hour before surgery; OR
  - Ampicillin 2 G IM/IV given 30 minutes before surgery

If allergy to penicillin:
- Clindamycin 600 mg PO/IV given 1 hour before surgery PO or 30 minutes before IV; if parenteral dose used, follow with 150 mg PO/IV 6 hours later; OR
- Azithromycin or Clarithromycin 500 mg PO given 1 hour before surgery; OR
- Cephalexin 2 g PO given 1 hour

before surgery; OR
  - Cefazolin 1 g IV given 30 minutes before surgery
- Neutrophils <1.0 x 10^9/L -
  - Give Meropenum 500 mg IV q6h, starting 30 minutes before surgery and continuing until afebrile
- Platelets 40 - 75 x 10^9/L - Platelet transfusions are optional; consider administering preoperatively and 24 hours later. Additional transfusions are based on clinical course.
- Platelets < 40 x 10^9/L - Platelets should be transfused 1 hour before procedure, immediately obtain platelet count, transfuse regularly to maintain counts above 30-40 x 10^9/L until initial healing has occurred.

During the period of dental work and upon completion, the dental team must stay in close communication with the oncology team, to properly and safely coordinate the overall plan for patient care. See Table 4.1.

4.3 Dental Management Following Chemotherapy and/or Radiotherapy

Upon completion of the cancer treatment, the patient may require further dental work. Dental work may or may not be related to the cancer or cancer treatment. The dental team must continue to communicate with the oncology team, to ensure that all relevant clinical information is considered prior to future dental work.

Patients treated for head and neck cancers should visit their dentist every 4 months over the 2 years following radiotherapy, for regular cleaning and assessement. These patients will also have follow-up care annually by the prosthodontist. After 2 years post-radiotherapy, patients may return to annual dentist visits or as needed. Patients should be on daily oral fluoride tablets.

One issue of concern to dentistry is the development of osteonecrosis of the jaw (see Part 7.20) in some patients under treatment with bisphosphonate agents, such as Pamidronate. The dental team must be aware if a patient has received or continues to receive these drugs before planning any major dental surgery, such as a tooth extraction.

Planning may need to be altered based on individual patient outcomes from cancer treatment. This may continue to be an issue for the remainder of some patients' lives.

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Part 5. Referral Information

5.1 Community Dentist

Patients who are scheduled to receive cancer treatment with a low risk of oral complications may be assessed by their family dentist, preferably well in advance of the planned first treatment date. Community dentists may also be contacted by the patient's oncologist or the hospital-based dentist for an assessment referral. Some patients may require referral to an oral surgeon or oral pathologist.

General dental care and maintenance is not covered under MSI, although cancer treatments (especially radiation therapy) can have a significant effect on a patient's dentition. Cost for these services are the responsibility of the patient through their own means or through private dental insurance. These services are provided by the patient's own community dentist. Unfortunately, many patients are unable to afford proper dental care.

There is coverage under provincial health insurance (MSI) for oncologic dental prostheses and for extraction of teeth prior to cancer treatment (radiotherapy, chemotherapy or HSCT) through the cancer team's Maxillofacial Prosthodontist. Coverage for patients from other provinces must be arranged in advance, and may not be available. In some circumstances, the dental care may be provided by the oral maxillofacial (OMF) surgeon at CDHA dentist at no cost to the patient (on a case-by-case basis).

5.2 Hematopoietic Stem Cell Transplant Patients

Once it has been established that the patient will undergo a transplant, the BMT/HSCT coordinators send a referral to the CDHA Department of OMF Surgery. An appointment time is sent back to the coordinator who in turn phones the patient with the date and time. The coordinators attempt to organize other activities (ie. tests and appointments) on the same day as the dental appointment (VG Site) to decrease the number of visits.

After the patient is seen, a written consultation from OMF Surgery is sent back to the HSCT physician with recommendations. For uncomplicated oral care issues, the patient is generally referred back to their own dentist and has the dental work completed before transplant. If there are complicated issues, the CDHA OMF surgeon will contact the patient's dentist for further discussion. Some complicated dental work may be performed in the Department of Oral and Maxillofacial (OMF) Surgery at QEII.

Occasionally a patient does not have a dentist. The Department of OMF Surgery clinic does not have the personnel (i.e. general dentists) or equipment to provide general dental care to these patients. The Department of OMF Surgery will attempt to find a dentist for the patient in their own community (or near the VG Site if they are from a different location, but they are awaiting treatment). If the patient is unable to afford dental care, provincial health insurance (MSI) will occasionally cover some basic dental services but a predetermination is required and can take up to several weeks to obtain (which is unrealistic for the HSCT population).

There are general dentists who are willing to provide the necessary immediate oral care at no cost to pre-transplant patients who have no means of paying. The Department can sometimes arrange this on a per case basis. The HSCT co-ordinators occasionally have access to some funds for the necessary dental care. The Department of OMF Surgery may recommend tooth extraction for HSCT patients (and selected radiotherapy or chemotherapy patients), to ensure that all potential sources of odontogenic infection are removed regardless of a patient's ability to pay.

The initial consultation in the Department of OMF Surgery at QEII is a MSI insured benefit as are necessary extractions in selected cancer patients. There is no remuneration for consulting on or providing dental treatment for pre-transplant patients from New Brunswick or Prince Edward Island. These patients are not billed for the initial consultation. NB and PEI patients are billed for treatment rendered but the ability to pay is never a determinant in treating these patients. Patients who indicate that they are unable to pay are not billed.

5.3 Hematology/Medical Oncology Patients

Physicians may consult the Department of OMF Surgery as required, or the patient may be referred to their community dentist.

5.4 Head & Neck Cancer Patients

Before a head & neck cancer patient receives radiation treatment , they must have a dental assessment prior to radiotherapy. These patients are referred to a Maxillofacial Prosthodontist in the Otolaryngology Department (fax: 423-5001) for a thorough dental assessment. Appliances and other interventions may be recommended and produced by the Maxillofacial Prosthodontists. If extraction is necessary prior to treatment, extractions may be performed in the Department of OMF Surgery at the QEII, or the patient may be referred to their community dentist as appropriate.

6.1 Oral Hygiene

Guideline Suggestion:

Use of a uniform, systematic plan for oral care, along with standard educational approaches to help patients understand and cope with the symptoms of oral complications, is suggested. The comprehensive management plan(s) may reduce the severity of mucositis caused by chemotherapy or radiotherapy.

Level of Evidence: III

Grade of Recommendation: B

A systematic approach for mouth care is outlined in the Mouth Care Plans (Basic and Intensified), described in Appendix III.

Guideline Suggestion:

Patients on active chemotherapy or radiotherapy should be educated on appropriate mouth care practices[1] and encouraged to follow these practices during active treatment and recovery. Basic oral hygiene is particularly important for any patient who is immunocompromised.

Level of Evidence: III

Grade of Recommendation: B

Strict oral hygiene is important for patients with cancer.[2]

The major purposes of oral care are to maintain normal function of the oral tissues, to maintain comfort, and to reduce the risk of local and systemic infection.[3,4] The aims of care are well summarized by Daeffler[5]

1) Keep oral mucosa clean, soft, moist and intact thus preventing infection
2) Keep the lips clean, soft, moist and intact
3) Remove food debris/dental plaque without damaging the gingiva/ periodontum
4) Alleviate pain/discomfort thus enhancing oral intake
5) Prevent halitosis and freshen the mouth

Effective oral hygiene is important throughout cancer treatment and recovery, with emphasis on oral hygiene beginning prior to initiation of that treatment.[6-8] Primary preventive measures such as well-balanced nutritional intake, adequate oral hygiene, and early detection of oral problems are important pre-treatment interventions.

Mouth care should be planned daily on the basis of individual patient assessment.[9] Patients on active chemotherapy or radiotherapy should be educated on appropriate mouth care practice (including oral hygiene procedures) and encouraged to follow the practices during active treatment. (Appendix VI- Patient Education Materials).

The patient should be informed of the rationale for the oral hygiene program as well as the potential side effects of cancer chemotherapy and radiation therapy.

The provision of regular, organized oral care is extremely important in reducing the incidence and severity of oral complications from cancer treatment.

6.1.1 Frequency of oral care

The vital factors in oral care are the frequency, thoroughness and consistency with which it is performed. To prevent complications, the frequency of care is more important than the agents employed.

On the basis of evidence from Howarth[10], Beck[11], and Dudjack[12], and in the absence of more recent research, Krishnasamy[13] proposed various frequencies of oral care delivery according to the patient's condition:

- Care every 4 to 6 hours may reduce the patient's potential for infection from microorganisms.
- Care every 2 hours may reduce mouth care problems and may enhance patient comfort by keeping membranes moist.
- Care every hour (or more frequently) is appropriate for patients requiring oxygen therapy, patients who breathe through their mouths, patients with oral infections, unconscious patients, and patients with severe mucositis.

6.1.2 Flossing, Brushing and Rinsing

A basic regimen of oral care, including flossing, teeth brushing, and rinsing, is essential to minimize the risk of developing oral complications.

Flossing and brushing are two of the most effective ways to remove dental plaque. Plaque is the buildup of debris on tooth enamel. Accumulated dental plaque contributes significantly to inflammation of the gingiva.[14]

6.1.2.1 Flossing

Flossing is important for oral hygiene as it allows a patient to clean the surfaces between the teeth. Many people do not floss because the technique is difficult to master, time-consuming, and, if improperly performed, can cause trauma to the tissues. If flossing causes bleeding of the gums which does not stop after 2 minutes, it should be discontinued until the platelet count increases to 20 x 10^9/L. Because of possible trauma to the gums, patients who have not flossed routinely before cancer treatment should not begin flossing at this time, unless suggested by the dentist or dental hygeinist.

Waxed and unwaxed floss are equally effective, but waxed floss may be easier to use and minimize trauma to the gingiva. To improve patient compliance however, the type of floss used by the patient prior to their cancer should be continued. Using dental floss daily rather than twice a day minimizes trauma to the gingiva. Flossing should be performed before bedtime brushing for optimal effectiveness.[15,16]

6.1.2.2 Brushing

A small, soft-headed, rounded-end, bristle toothbrush is the best tool for cleaning the teeth, even in the dependent patient.[5,12,16] Brushing should be performed four times a day with techniques that specifically maintain the gingival portion of the tooth and periodontal sulcus keeping them free of bacterial plaque. Rinsing the toothbrush in clean, hot water for 15 to 30 seconds before brushing will soften the brush and reduce risk for trauma. Brushes should be air-dried between uses.

The ease of tooth brushing may be influenced by various factors including gingival status, alignment of the teeth, personal motivation, patient fatigue, pain, and manual dexterity.[16] Toothbrushing is considered the most effective means of plaque removal, but it is not well tolerated in severe mucositis.

If the gingival tissue bleeds for more than 2 minutes, brushing may be discontinued and the teeth cleaned with moist gauze wrapped around the finger or a foam swab. If this is too painful (even with analgesia) or if it causes the gingival tissues to bleed, attempt rigorous rinsing. Once the platelets are $\geq$20 x 10^9/L, brushing may be resumed.

Although toothbrushing is undoubtedly better at removing plaque when used appropriately, a foam swab is able to remove some plaque from some oral areas.[17,18] Using a foam swab may reduce plaque and control gingivitis as an alternative when toothbrushing

cannot be performed. Additionally, foam swabs have the potential to stimulate saliva production and improve vascularity through gentle massage. Even if they may be useful in cleansing soft tissues, foam swabs are ineffective at cleansing tooth surfaces.

Clearly it is essential that debris and plaque are removed. The tooth cleaning process should not, however, cause further damage. Irrigation of the oral cavity can be useful in removing large food particles and debris although, alone, it will not remove all plaque from the gingival sulci. While irrigation may be useful in healthy individuals its value/ effectiveness in cancer patients is unknown. Some authors have identified possible harmful effects including formation of periodontal abscess and possible penetration of the oral tissue by bacteria and other particle matter. Irrigation may cause further damage to friable mucosa; care must also be taken to prevent the spread of infection.

Electric toothbrushes were developed in an attempt to make daily oral hygiene easier to perform, thereby improving patient compliance. They are popular and widely available with several different types of brushing motion, head design and bristles. The head design and hard bristles of most electric toothbrushes are manufactured to make the head last longer but are rarely of the ideal shape/ texture for thorough cleaning of the teeth and gums. They may be more effective in removing plaque and decreasing gingivitis than regular toothbrushes. Electric toothbrushes cover more area faster, but they may also increase the potential for gum injury and bleeding.[19-20] The use of electric toothbrushes is generally not recommended for patients at high risk of oral complications of cancer therapy.

6.1.2.3 Fluoridated toothpastes and gels. Since the flavoring agents in toothpaste can irritate oral soft tissues, a toothpaste with relatively neutral taste should be considered. Toothpaste requires three key ingredients to be effective: a detergent to lower surface tension and loosen surface debris which is then more easily removed, a fine abrasive to cleanse the teeth, and fluoride to prevent cavities. Fluoride is incorporated in hydroxyapatite reducing its solubility in acid and also enhancing remineralization when pH rises, this is probably the single most important intervention in the prevention of radiation-induced damage. Furthermore, fluoride inhibits bacterial metabolism thus lowering acid production and so can almost eliminate dental caries and tooth loss following irradiation of the head and neck.

Patients with receding gums should choose a low- or moderately-abrasive toothpaste to avoid abrading the exposed roots of their teeth. If the teeth are sensitive, patients can use a desensitizing toothpaste, such as Sensodyne.

6.1.2.4 Rinsing

Rinsing the oral cavity after flossing and brushing helps to maintain the moisture in the mouth, removes the remaining debris and toothpaste, and reduces the accumulation of plaque and infection. The patient should rinse, swish and spit at least 1 tablespoon (15mL), of rinse solution several times after each brushing. Rinsing without brushing can be repeated as often as necessary to maintain oral comfort. The patient should rinse mouth thoroughly using an alternative ballooning and sucking cheek motion to force mouth rinse solution between the teeth. If unable to do this, patients can tilt or rock the head from side to side prior to expectorating.

6.1.3 Mouth Rinse Solutions

Best Practice Statement:

Patients should be encouraged to thoroughly rinse out their mouths using a mouth rinse solution. Water, club soda, normal saline or sodium bicarbonate solution may be considered as reasonable options for mouth rinse solutions. Commercial solutions with hydroalcoholic base or astringent properties should be discouraged for routine mouth rinse during active cancer therapy.

To date, no research has demonstated the benefit of one rinsing solution over another and therefore they will all be discussed. It is recommended that patients be given their choice of rinse solution, to optimize patient compliance with oral hygiene practice.

Mouth rinse solutions should be nondehydrating to promote the safe removal of loose debris and to moisten and soften the oral mucosa. Suggested rinse solutions include **tap water** (or **bottled water** in areas where tap water may be contaminated), **saline** and **sodium bicarbonate** mouthwash. **Carbonated soda water** may be used as a simple, commercially-available substitute for other mouth rinse solutions. Club soda is inexpensive, and simple for patient use, making this alternative an attractive option for routine patient mouth care. A new can or bottle should be opened at least once every 24 hours, to avoid oral infection from a mouth rinse which has been open for possible contamination for more than a day.

Sodium chloride 0.9% (**saline** or NaCl) is not an irritant. Use of saline as a mouth rinse may be more effective than a regimen using a more astringent mouthwash. This solution is prepared by adding approximately ½ teaspoon (2.5mL) of table salt to 8 oz. of water. Mixing this as a stronger solution is not recommended, since it may harm mucosal tissue. Saline can be administered at room or refrigerated temperatures, depending on patient preference. Sodium chloride rinse solution should be prepared fresh at least once daily. The patient should rinse and swish approximately 1 tablespoon (15mL), followed by expectoration; this can be repeated as often as necessary to maintain oral comfort. Saline solution can enhance oral lubrication directly as well as by stimulating salivary glands to increase salivary flow.

Sodium bicarbonate ($NaHCO_3$) is a non-irritating compound that reduces the viscosity of saliva. Sodium bicarbonate (baking soda) neutralizes the acidic oral environment. The alkaline environment from sodium bicarbonate allows bacteria to multiply, which may have detrimental effects on the mucosa. This solution is prepared by adding ½ teaspoon of baking soda to 8 ounces of lukewarm water. Stronger solutions may be irritating to the oral mucosa and are not recommended. Patients sometimes report an unpleasant taste with sodium bicarbonate preparations, which may impact on subsequent compliance.[21] Sodium bicarbonate rinse solutions should be prepared fresh at least once daily and can be used cold or room temperature.

The mouth rinse solution should be prepared **at least once daily** (to avoid the risk of contamination). If a commercial product is used, a new bottle should be used every 24 hours.

The use of **hydrogen peroxide** as a mouth rinse has no scientific or clinical base, and controversy surrounds its use as it impedes granulation of new tissue. Hydrogen peroxide solution should only

be used for 1 to 2 days if absolutely necessary to remove necrotic material. More extended use may impair timely healing of mucosal lesions. It is both bacteriostatic and hemostatic, but its antibacterial properties may promote fungal overgrowth and may inhibit mucosal tissue granulation in patients with oral lesions.[22-24] Patients find it highly astringent, exacerbating a dry mouth, and unpleasant tasting.[22] Hydrogen peroxide **should not** be used as a mouth rinse.

Commercial mouthwashes with hydroalcoholic base or astringent properties are not recommended for patients with oral problems because they have the potential to cause irritation and hypersensitivity stomatitis through erythema, ulceration, and epithelial sloughing.[25] These clinical reactions may be caused by oils, astringents, alcohol, and antiseptics, as contents of commercial products. These products may be sweetened with saccharin and may contain coloring agents. They may also contain other aromatic substances.[25]

Lemon leads to tooth decalcification and overstimulation of salivary glands resulting in rebound xerostomia. Lemon-based products **should not** be used for mouth care.

6.2 Debriding

Tissue should not be debrided unless absolutely necessary (ie. loose tissue causing gagging or choking). Do not remove tissue that is still attached or hanging unless it is posing a risk. If after cleaning and rinsing, debris is not removed, rinse vigorously with soda water or the preferred mouth rinse solution.

Hydrogen peroxide is NOT recommended. If ongoing crusting and hemorrhagic debris does not dislodge after repeated use, the benefits of 1:1 hydrogen peroxide (3%)and water (or normal saline) may be considered.

6.3 Lip Care

Dry lips may be coated with either an oil-based lubricant or a water-based lubricant to keep the lips moist. Dry lips can become cracked and uncomfortable, and this condition may inhibit proper oral hygiene and eating. Oil-based lubricants such as petroleum jelly, mineral oil, and cocoa butter are effective on the lips but should be avoided on the inside of the mouth because of the danger of aspiration. Lanolin-based creams and ointments may be more effective in protecting the lips against trauma (e.g. from heat or cold, hard foods, etc.)[26], but are contraindicated in patients allergic to wool products.

Patients should be encouraged not to touch their lip lesions. Water-soluble lubricants can be used inside and outside of the mouth. These lubricants can be used during oxygen therapy, without risk of aspiration. They should be applied more frequently, before meals, after cleaning and at bedtime. Examples of water-soluble lip lubricants are products compounded with Glaxal Base or Derma Base (eg. K-Y Jelly, Dermasone). Examples of non-soluble lubricants are lanolin, petroleum jelly, mineral oil and cocoa butter.

6.4 Eating

Patients should be discouraged from eating foods which are abrasive, rough, spicy, acidic, or very hot. Alcohol and tobacco can be irritating to the oral tissues; patients should be encouraged to limit or stop the use of these substances and others which irritate the mouth. High-density and high-fibre foods help to clean teeth and massage the gums. Patients may be encouraged to eat these foods, as well as foods high in protein and

vitamins B and C. Adequate fluid intake is important to maintain good oral hygiene. Patients should be encouraged to drink plenty of fluids, with a target intake of 2 liters /day.

If a patient experiences oral complications, bland foods are recommended. TPN (total parenteral nutrition) or G-tube (gastrostomy tube) feeding may be needed for patients who are unable to eat or swallow. Topical anesthetics, applied 20 to 30 minutes before eating, (or topical analgesics applied 1 hour before eating) may provide enough comfort for the patient to be able to eat or drink. The numbing effect of the anesthetic commonly lasts 1-2 hours after the application. The gag reflex should be checked prior to eating or drinking, in case the patient swallows the anesthetic, by accident or instead of spitting it out.

6.5 Management Plans

Guideline Suggestion:

Use of a uniform, systematic plan for oral care, along with standard educational approaches to help patients understand and cope with the symptoms of oral complications, is suggested. The protocol should be multidisciplinary. One component of the protocol should be the use of a soft toothbrush that is replaced on a regular basis. The comprehensive management plan(s) may reduce the severity of mucositis caused by chemotherapy or radiotherapy.

Level of Evidence: III

Grade of Recommendation: B

Best Practice Statement:

For routine care, the oral complication treatment components are compiled into Mouth Care Plans. The Basic Mouth Care Plan is used for most patients. The Intensified Mouth Care Plan is used for patients as they develop intermediate to severe stomatitis (on the Stomatitis Staging System scale for screening), returning to the Basic Mouth Care Plan when stomatitis and other symptoms have resolved. These Mouth Care Plans should be integrated into hospital nursing care plans for cancer patients and used as a basis for health education of ambulatory patients.

6.5.1 BASIC MOUTH CARE PLAN

A basic regimen of oral care, for patients without oral complications, is essential to minimize the risk of developing future complications. The interventions described for basic mouth care should be considered for all patients who have cancer. They should be initiated before treatment begins and continued until the risk of side effects or oral complications is over. Basic mouth care practices are for the patient with Grade 0-1 stomatitis (rated by the CTC) . Key points are listed in Table 6.1.

6.5.2 INTENSIFIED MOUTH CARE PLAN

Intensified mouth care practices are for the patients who have been graded on the CTC as 2 or greater. These practices build on those of basic mouth care practices. Key points are listed in Table 6.2.

Patient Education

Patients who are to receive chemotherapy or radiotherapy should begin their education about possible oral complications and preventive mouth care practices as they begin their treatment teaching.

The importance of brushing, even with discomfort should be normalized and emphasized so that patients have the expectation of continuing the brushing with pain should it occur.

Table 6.1 Basic Mouth Care Plan	
Flossing	• Flossing with dental floss allows a patient to clean surfaces between the teeth • Flossing is usually done before brushing, and before going to bed. • The patient should continue their flossing practices, using the same type of dental floss as they have done in the past. • If flossing causes bleeding of the gums which does not stop after 2 minutes, it should be discontinued. Flossing may be restarted when the platelet count is $\geq 20 \times 10^9$/L, or as instructed by their cancer care team. • Patients who have not flossed routinely before cancer treatment should not begin flossing at this time • Patients with cancers in the mouth may not be able to floss
Brushing	• Use a small, soft-headed, rounded-end, bristle toothbrush (electric toothbrushes are not preferred), and a fluoridated toothpaste or gel (preferably with a neutral taste) • Brush teeth 4 times daily, within 30 minutes after eating and before bed. Brush after flossing • Rinse toothbrush in hot water to soften it before using • Brush tongue gently from back to front • Rinse brush after using in hot water. Air dry. • Change toothbrush when bristles are not standing up straight (about once per month) <u>Patients with Head & Neck Cancers</u> • Brushing may not be appropriate because of tumour involvement. Patient may attempt to clean teeth with a moist gauze wrapped around the finger or a foam swab soaked in rinsing solution, if able. Otherwise patient should rinse mouth several times with rinsing solution. <u>Dentures</u> • Remove dentures, plates and prostheses before beginning mouth care. • Rinse mouth thoroughly with rinse solution. • Brush and rinse dentures after meals and at bedtime. Rinse with rinsing solution before placing in mouth. Remove from mouth for long periods (at least 8 hours/24). Soak in rinsing solution.
Rinsing	• Rinsing the oral cavity helps to maintain the moisture in the mouth, removes the remaining debris and toothpaste, and reduces the accumulation of plaque and infection • Rinse vigorously several times after brushing and flossing, using one of the rinsing solutions
Lip Care	• Coat lips with an oil-based or water soluble lubricant to keep them moist. Water soluble lubricants may be used inside and outside the mouth, and can be used with oxygen, since there is no risk of aspiration. • Apply the lubricant after each cleaning,at bedtime, and as needed. Water-based lubricant needs to be applied more frequently.
Eating	Avoid abrasive, rough, spicy, acidic and hot foods. All irritants should be avoided, especially alcohol and tobacco. Eat soft foods. Avoid foods containing a lot of sugar, and really cold foods. Encourage high-density and high-fibre foods to clean teeth and massage gums. Encourage a well-balanced diet, high in protein, vitamins B & C. Encourage a fluid intake of at least 2 litres per day to keep mucous membranes moist.

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Table 6.2 Intensified Mouth Care Plan	
Flossing	• Continue until discomfort becomes too great • Discontinue flossing if gums bleed for longer than 2 minutes. Advise patient to try to begin again when platelet count rises >20 x 10^9 cells/mL.
Brushing	• Use ultra soft toothbrush (Butler 435 stocked on some inpatient units) • Encourage patient to continue brushing through treatment even when it causes discomfort. If unable to tolerate brushing after benefits are reinforced and weighed against the detriments, try to clean teeth with a moist gauze wrapped around finger or a foam swab soaked in rinsing solution. • Consider the use of a topical analgesic q 4-6 hours to promote more thorough tooth brushing when continuous pain is present. Oral analgesics (opioids) should be given 60 minutes before brushing. • Consider a topical anesthetic before brushing to minimize pain. • If bleeding does occur, encourage more gentle brushing. If bleeding does not stop after 2 minutes, consider cleaning with gauze, toothette or vigorous rinsing (with rinsing solution). Restart brushing when platelet count > 20 x 10^9 • If the gingival tissue bleeds, clean teeth with a moist gauze wrapped around the finger or a foam swab • If there has been an oral infection, use a new toothbrush after infection is resolved. • Dentures Keep out of mouth as much as possible
Rinsing	• Perform in place of brushing if patient absolutely unable to brush. • As well as after meals, encourage rinsing every 1-2 hours while awake, and every 4 hours through the night if awake (to minimize complications of decreased saliva). • If unable to clean using toothette or gauze or swishing (or tilting head), syringe rinsing solution into different areas of mouth if platelet level is not too low.

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Part 7. Clinical Manifestations and Management of Oral Complications from Cancer and Cancer Treatment

7.1 Introduction

Mouth care practices, as described in Part 6, should be continued through the period of cancer treatment and recovery, as appropriate to the level of oral complications experienced by the patient. In addition to the mouth care practices, patients may require symptom management and treatment of different problems. Treatment of the problems may require different approaches for different patients. Often more than one problem occurs concurrently, and management may be complicated and may require careful integration.

7.2 Mucositis

The terms "oral mucositis" and "stomatitis" are often used interchangeably at the clinical level, but do not reflect identical processes. Oral mucositis describes inflammation of oral mucosa resulting from chemotherapeutic agents or ionizing radiation. Mucositis typically manifests as erythema or ulcerations. It may be exacerbated by local factors. Stomatitis refers to any inflammatory condition of oral tissue, including mucosa, dentition/periapices and periodontium. Stomatitis thus includes infections of oral tissues, as well as mucositis as defined above. [1-3]

Oral mucositis is a major cause of morbidity in cancer patients and results from the exposure of the underlying connective tissue to the oral environment and the tissue's reaction to the insult. Cancer therapy-induced tissue damage leading to mucositis can occur through either direct or indirect stomatotoxicity. Since cellular replication is inhibited, inadequate numbers of cells are available to maintain mucosal integrity. The mucosa becomes thin, inflamed and eroded, as outlined in Part 2.

Initially patients may complain of a mucosal tenderness, a burning sensation in their mouth. This commonly progresses to increased sensitivity to heat and cold, and to spicy and salty food. The ulcerations are usually painful, causing restrictions in oral intake and, importantly, act as sites of secondary infection and portals of entry for the endogenous oral flora.

Mucositis appears clinically as erythematous or diffuse ulcerative lesions. These lesions develop primarily on the non-keratinized tissues such as the buccal and labial mucosa, the ventrolateral surface of the tongue and the floor of the mouth. The hard palate, attached gingiva, and the dorsal surface of the tongue are rarely subject to mucositis but may become painful. [4]

The overall frequency of mucositis varies and is influenced by the patient's diagnosis, age, level of oral health, the type, dose, and frequency of drug administration and/or the dose and field of radiation therapy. The presence of dental appliances has the potential to irritate the oral mucosa and produce breaks in the integrity of the mucosa. Increases in the use of alcohol and tobacco have also been implicated in increasing the incidence of mucositis.

Oral mucositis is a distressing toxic effect of systemic chemotherapy with many commonly utilized drugs and of head and neck irradiation in patients with cancer. [5-11] Chemotherapy alters the integrity of the mucosa. Mucositis can be the major dose-limiting toxicity during the administration of certain types of chemotherapy, especially 5-fluorouracil, methotrexate and doxorubicin.

Chemotherapy-induced mucositis begins shortly after therapy, reaching a peak within 1 to 2 weeks after treatment and slowly receding unless complicated by infection, hemorrhage or repeat drug administration.

The origin of radiation-induced mucosal lesions is iatrogenic in nature, although further development of mucositis is essentially influenced by infection.

Mucositis is the result of these atrophic changes in the epithelium related to the decreased cell renewal. Mucosal reactions in patients receiving radiation treatment for head and neck cancer are regarded as unavoidable side effects, and generally occur 5 to 7 days after initiation of radiation therapy. The degree of mucositis experienced is determined by the treatment dose, radiation field size and fractionation schedules prescribed for individual patients. It occurs after a dose of approximately 10 Gray (1000cGy). Mucositis usually resolves two to three weeks after the termination of radiation therapy if infection and additional trauma are avoided[12-16].

Oral mucositis in cancer patients produces clinically significant toxicities that require multiprofessional interventions.[17-24] The lesion can increase risk for systemic infection, produce clinically significant pain, and promote oral hemorrhage. Local infections may become systemic and life-threatening, especially in immunocompromised patients such as HSCT patients. Once mucositis has developed, its severity and the patient's hematologic status govern appropriate oral management.[17,22] Meticulous oral hygiene and management of symptoms are essential.

The prevention and management of mucositis are illustrated in Figures 7.1, 7.2 and 7.3 for low, intermediate and high risk patients respectively.

7.2.1 Mucositis Prevention

Best Practice Statement:
Patients with oral mucositis require appropriate therapeutic intervention(s) to prevent symptoms.

Prevention is the most effective strategy for mucositis. Oral care protocols generally include procedures for cleansing the oral mucosa (with minimal trauma), maintaining lubrication of the lips and oral tissues, and relieving pain and inflammation (Appendix III). It should be noted that some agents for prevention of mucositis may continue to be used during treatment if mucositis occurs.

7.2.1.1 Benzydamine

Guideline Recommendation:
Benzydamine is recommended for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiotherapy.
Level of evidence: I
Grade of recommendation: A

Benzydamine hydrochloride is a topical nonsteroidal drug, with anti-inflammatory, analgesic, anesthetic and antimicrobial properties. It has also been shown to inhibit proinflammatory cytokines, such as TNF-α. Clinical trials have shown that benzydamine can reduce the severity and frequency of oral mucosal ulcers and decreases pain associated with radiation-induced oral mucositis[25-28].

7.2.1.2 Radiotherapy Delivery

Guideline Recommendation: *Midline radiation blocks and three-dimensional radiation treatment to the oral cavity should be used where possible, to reduce mucosal injury.*
Level of evidence: II
Grade of recommendation: B

Although clinical trials addressing the effect of radiotherapy planning have not

Table 7.1: Agents for Mucositis Prevention	
Cryotherapy	Oral Cryotherapy (sucking ice chips) with 5FU bolus chemotherapy, high dose Melphalan used in HSCT conditioning regimen
Biological Response Modifiers	Keratinocyte Growth Factor 1 (KGF-1)- Palifermin (Kepivance) Keratinocyte Growth Factor 2 (KGF-2) Interleukin-11 Transforming Growth Factor Beta-3
Topical Analgesics	Benzydamine HCl topical rinse (e.g. Tantum™)- to prevent radiation-induced mucositis
Other Agents Under Investigation	Amifostine Topical Vitamin E, Topical Betacarotene Prostaglandin E (PGE2) Lozenge Kamillosan liquidum oral rinse Glutamine Granulocyte Colony Stimulating Factor (GCSF) Sodium Alginate Misoprostol (topical) Low Energy Laser Therapy Radiation Shields Protegrins/Defensins Lysofiline

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been large, it has been shown that the use of midline radiation blocks and the use of three-dimensional treatment delivery (which reduces irradiation to a larger volume of mucosa) may reduce oral mucosal injury[29,30].

7.2.1.3 Cryotherapy

Guideline Recommendation:

Patients receiving 5-fluorouracil-based chemotherapy should be treated with oral cryotherapy (ice chips in the mouth for 30 minutes starting 5 minutes before chemotherapy administration) to prevent stomatitis. This recommendation should be suspended if oxaliplatin is included in the chemotherapy regimen.

Level of Evidence: II

Grade of Recommendation: B

Although mucositis continues to be one of the dose-limiting toxicities of fluorouracil (5-FU), cryotherapy may be an option in prevention of oral mucositis.[31-34] It may ameliorate mucositis caused by agents such as 5-Fluorouracil (5-FU) by reducing vascular delivery of these toxic agents to replicating oral epithelium. In addition, use of cold packs or frozen ice bags has successfully relieved fluorouracil-related side effects occurring at other sites including lips, skin, and groin area. Patients are instructed to swish ice chips in their mouths for 30 minutes, beginning 5 minutes prior to bolus 5-FU administration. It is not practical to consider cryotherapy with infusional 5-FU, however. *(Note: an exception is cryotherapy for regimens containing both 5-FU and Oxaliplatin. Cold-induced dysaesthesia from Oxaliplatin is a common and preventable toxicity of this chemotherapy agent)*

Guideline Suggestion:

Patients receiving high-dose melphalan as part of a conditioning regimen for stem cell transplant should be treated with oral cryotherapy to prevent oral mucositis.[23]

Level of Evidence: II

Grade of Recommendation: A

In the 2005 update to the Multinational Association of Supportive Care in Cancer (MASCC) guidelines, emergent evidence was reviewed to suggest that cryotherapy may also be an effective strategy for oral mucositis prevention in stem cell transplantation patients receiving high-dose melphalan as part of their conditioning regimen. It is not known if cryotherapy is effective preventive therapy with other conditioning regimens.

7.2.1.4 Human Keratinocyte Growth Factors

Guideline Recommendation:

In patients with hematological malignancies receiving high dose chemotherapy and total body irradiation with stem cell transplant, Keratinocyte Growth Factor-1 (Palifermin) in a dose of 60 µg/kg/day for 3 days prior to conditioning treatment and for 3 days post-transplant is recommended for the prevention of oral mucositis. [231]

Level of Evidence: I

Grade of Recommendation: A

Recombinant human keratinocyte growth factor 1 (rHuKGF-1; palifermin) was evaluated in a randomized double-blind placebo-controlled trial involving patients undergoing autologous transplantation for a variety of hematologic malignancies, palifermin 60 mcg/Kg/day was given for 3 days before conditioning and 3 days after transplant[35]. Results showed a reduction in duration of severe mucositis (*3.7 vs 10.4 days; P < 0.001*), reduced incidence of grade 4 mucositis (*20% vs 62%; P < 0.001*), and reduced use of opioid analgesics (*212 vs 535 mg morphine equivalents median usage per patient; P < 0.001. 7 vs 11 days median duration of opioid use per patient; P < 0.001*). Based on this pivotal trial in 212 patients, palifermin has been approved for use in Canada. There was no change in survival between the groups (indicating that palifermin did not reduce the effectiveness of the transplant intervention). Adverse effects from palifermin included increased skin erythema, pruritus, edema, tongue "feeling thick," taste disturbances (*26% vs 3%*), and transient asymptomatic increases of serum lipase (*77% vs 67%*) and serum amylase (*32% vs 25%*).

In another multicenter, randomized, double-blind, placebo-controlled Phase II trial[36], palifermin was studied in patients with head and neck cancer who received standard or hyperfractionated radiotherapy with concomitant chemotherapy. The palifermin-treated group had a lower incidence and shorter duration of mucositis compared with the group that received placebo.

Human keratinocyte growth factor 2 (KGF-2; repifermin) was evaluated in a Phase II trial[37] with 42 patients who received conditioning regimens with chemotherapy before undergoing autologous stem cell transplant. This trial was withdrawn due to poor performance of the new agent[231].

7.2.1.5 Agents Which Have Not Proven to be Effective for Prevention of Mucositis

Many agents and protocols have been promoted for management or prevention of mucositis. Several of these have been tested and proven to be ineffective in trials conducted to date. These are identified in a series of guideline recommendations below, adapted from the MASCC guidelines[38], updated in 2007[231].

Chlorhexidine

Guideline Recommendation:

*Chlorhexidine should **not** be used to prevent oral mucositis in patients with solid tumors of the head and neck who are undergoing radiotherapy.*

Level of Evidence: II

Grade of Recommendation: B

If tolerated by the patient, chlorhexidine may be used as part of an oral care plan to help prevent dental caries (usually on the advice of a dentist). Several clinical trials have failed, however, to demonstrate that chlorhexidine is effective in preventing[39-41] or treating[42,43] oral mucositis (see section 7.5.1.1).

Sucralfate

Guideline Recommendation:

*Sucralfate should **not** be used for the prevention of radiation-induced oral mucositis.* [231]

Level of Evidence: II

Grade of Recommendation: A

Sucralfate, an anti-ulcer drug, binds to ulcerated tissue. Oral sucralfate forms an adhesive, paste-like substance and attaches to proteins in the damaged mucosa, forming a protective coating that prevents further mucosal damage. Sucralfate is available in tablet form and must be dissolved in water to make an oral rinse that is swished and expectorated or swallowed. The mixture must be refrigerated and shaken well prior to use.

Even though sucralfate has been used as a mucosal coating agent, it has not been found to have any effect on mucositis prevention or treatment.[44-51]

Antimicrobial Lozenges

Guideline Recommendation:

*Antimicrobial lozenges should **not** be used for the prevention of radiation-induced oral mucositis.* [231]

Level of Evidence: II

Grade of Recommendation: B

Acyclovir

Guideline Recommendation:

*Acyclovir and its analogues should **not** be used routinely to prevent mucositis.*

Level of evidence: II

Grade of recommendation: B

While acyclovir has not proven to be useful for prevention of mucositis, it may be considered as a treatment option for systemic viral infection.

Systemic Glutamine

Guideline Recommendation:

*Glutamine should **not** be used routinely to prevent mucositis.* [231]

Level of evidence: II

Grade of recommendation: C

GM-CSF Mouthwashes

Guideline Recommendation:

*Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) mouthwash formulations are **not** recommended for prevention of mucositis in patients undergoing hematopoietic stem cell transplant.* [231]

Level of evidence: II

Grade of recommendation: C

Pentoxifylline

Guideline Recommendation:

*Pentoxifylline is **not** recommended for prevention of mucositis in patients undergoing hematopoietic stem cell transplant.*

Level of evidence: II

Grade of recommendation: B

7.2.1.6 Other Agents for Prevention of Mucositis (Insufficient Evidence)

Although not adequately supported by controlled clinical trials, allopurinol mouthwash[52] and vitamin E[53] have been cited as agents that improve mucositis. Topical application of phytochemicals such as betacarotene[54] also may protect the oral mucosa. A single trial of Saforis (L-glutamine) showed reduced mucositis; further trials are underway[231]. Another

trial of N-acetylcysteine mouth rinse (RK-0202) demonstrated reduced mucositis in head and neck cancer patients[231].

Kamillosan liquidum oral rinse is also used in preventing or reducing the intensity of mucositis in patients with head and neck cancer receiving radiation and chemotherapy. Kamillosan liquidum solution is prepared from the flower of the chamomile plant. Kamillosan solution has an anti-inflammatory action and appears to accelerate re-epithelialization of desquamated tissue.

Prostaglandin E (PGE2) [55-57] also has been given to patients in lozenge form to protect the oral mucosa from injury. It is proposed that PGE2 reduces cell breakdown by protecting the DNA. It has less systemic effect by topical application and has been noted to reduce the amount of desquamation in some cases. It has also been claimed to reduce the pain and the inflammation, and to heal the ulcer within 5-15 days.

Usage of granulocyte colony-stimulating factor (G-CSF) [58-63], a hematopoietic growth factor, reduces the severity and duration of chemotherapy-induced neutropenia. It has been suggested that reduced neutropenia is associated with less severe mucositis, but research results have been conflicting on the value of G-CSF for treatment or prevention of oral mucositis.

Table 7.2: Agents for Mucositis Management (Stepped Approach)

1. Mucosal Coating Agents	Alumina suspension (Amphojel™)- constipating effects Magnesia Suspension (Milk of Magnesia™)- laxative effects Alumina and Magnesia Suspension (Maalox™)- balanced bowel effects Attapulgite suspension (Kaopectate™)- mild constipating effects • May use 5-10mL 4-6 times daily to coat the mucosal surfaces
2. Water-Soluble Lubricating Agents	Artificial Saliva (e.g. Moi-Stir™, Salivart™)- 1-2 mL PRN OraBase™
3. Topical Analgesics/ Anti-inflammatory Agents	Benzydamine topical rinse (e.g. Tantum™)- No effect on gag reflex • Rinse mouth with 10-15 mL q 4-6 hours; swish around mouth and spit out • May have a drying effect (from alcohol in formulation) May consider systemic analgesics (e.g. Acetaminophen) or non-steroidal anti-inflammatories (e.g. ibuprofen, naproxen)- unless contraindicated for patients at risk of febrile neutropenia
4. Topical Anesthetics/ Pain Relief Mouthwash Formulations	Lidocaine: Viscous, Ointment, Sprays (e.g. Xylocaine™)- Xylocaine Viscous is a thick paste, most patients dislike the sensation of this viscous product • Swish and swallow slowly or spit out of mouth 5-10 mL q4h PRN; may inhibit gag reflex- do not eat or drink for at least 30 minutes after dose • Anesthetic effects occur in 5 minutes and last 20-30 minutes Diphenhydramine liquid (e.g. Benadryl™)- may cause sensitization of the mucosal tissue; used in patients who cannot tolerate other anesthetics • Swish and swallow 5-10 mL q4h PRN; Use non-alcoholic liquid formulation • Lidocaine and/or Diphenhydramine are components of the Pain Relief Mouthwash formulations
5. Systemic Analgesics	Opioid Drugs: Oral, IV Bolus Morphine or Hydromorphone Continuous infusion, PCA dosing of Morphine or Hydromorphone for severe pain- Use according to institutional policy
6. Cellulose Film-forming Agents	Film-forming Agents (e.g. Film-forming Hydroxypropylcellulose (Gelclair™), when available in Canada; or other available products)

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Figure 7.1 Prevention & Management of Oral Complications in Low Risk Patients

LOW RISK (10%)
Patients treated with Adjuvant/Palliative Chemotherapy

SCREENING

Screen each patient with Stomatitis Staging System (SSS) scale

Pre-treatment Dental Exam recommended

PREVENTION

Prevention
Oral cryotherapy (ice chips) for 30 minutes, beginning 5 minutes prior to 5-Fluorouracil administration

Use Basic Mouth Care Plan: (See Table 6.1)
- Drink plenty of fluids (2L/day)

Follow oral care Recommendations of Dentist
- Dentist may order Chlorhexidine for dental caries prevention when there is no mucositis

Patient Education on mouth care and how to manage oral complications from cancer therapy

ASSESSMENT

If **mucositis** or other oral complications are identified from routine screening, and become a focus of care, assess with the SSS scale and other sections on the Mouth Care Record until symptoms resolved

MANAGEMENT

Stepped Approach for Management

1. Mucosal coating agent (i.e. attapulgite [Kaopectate™] antacid suspensions)- to provide a temporary physical barrier
   - **Do NOT use Chlorhexidine** if there is mucositis
2. Water-soluble lubricating agents (e.g. artificial saliva, KY Jelly, OraBase)- to moisten the mucosa
3. Topical analgesic (i.e. benzydamine)- to reduce pain by anti-inflammatory effect
4. Topical anesthetics (e.g. lidocaine)- to reduce pain by numbing the mouth
   - May use Pain Relief Mouthwash if needed for oral pain (combination of mucosal coating agent and topical anesthetic) See Table 7.4
5. Systemic analgesics (oral, IV bolus morphine or hydromorphone) for severe pain

May add oral Fluconazole for prevention or treatment of oral fungal infection

Oral Infection
- See Table 7.6

Oral Hemorrhage:
- Treat with ice water and local pressure

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Figure 7.2 Prevention & Management of Oral Complications in Intermediate Risk Patients

INTERMEDIATE RISK (40%)
Patients treated with primary chemotherapy (e.g. Hematologic Malignancies) and some Gastrointestinal Cancer Chemotherapy

SCREENING

► Screen each patient with Stomatitis Staging System (SSS) scale

Pre-treatment Dental Exam required

PREVENTION

Prevention
Oral cryotherapy (ice chips) for 30 minutes, beginning 5 minutes prior to 5-Fluorouracil administration (unless Oxaliplatin will also be given)
Patient Education on mouth care and how to manage oral complications from cancer therapy

Basic Mouth Care Plan: (Table 6.1)
- Drink plenty of fluids (2L/day)

Follow oral care Recommendations of Dentist
- Dentist may order Chlorhexidine for dental caries prevention when there is no mucositis

ASSESSMENT

If **mucositis** or other oral complications are identified from routine screening, and become a focus of care, assess with the SSS scale and other sections on the Mouth Care Record until symptoms resolved

MANAGEMENT

- Increase to Intensified Mouth Care Plan if stomatitis worsens
  - Continue flossing unless bleeding (> 2 minutes)
  - Brush teeth gently with ultra soft toothbrush
  - Use mouth rinse solution q1-2hr (q4h during the night)
  - Referral to dietitian for any nutritional problems
  - Add antibiotics or other treatments as needed for additional symptoms

Stepped Approach for Management – below (see Low Risk)

1. Mucosal coating agent (i.e. attapulgite [Kaopectate™] antacid suspensions)
- **Do NOT use Chlorhexidine** if there is mucositis

2. Water-soluble lubricating agents (e.g. artificial saliva, KY Jelly, OraBase)

► 3. Topical analgesic (i.e. benzydamine)

► 4. Topical anesthetic (i.e. lidocaine)
- May use Pain Relief Mouthwash if needed for oral pain (Table 7.4)

5. Systemic opioid analgesics (oral, IV bolus morphine or hydromorphone) for severe pain

May add oral Fluconazole for prevention or treatment of oral fungal infection

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Figure 7.3 Prevention & Management of Oral Complications in Head & Neck Cancer (High Risk) Patients

SCREENING

Assess each patient with Mouth Care Record from beginning of treatment until all symptoms are resolved (no longer a focus of care)

Comprehensive dental exam before treatment

- Prosthodontic care prior to radiotherapy to oral cavity
- Eliminate oral disease before treatment (e.g. dental extraction of high-risk dentition) for radiotherapy patients

PREVENTION

Prevention- Patients on Radiotherapy

- Topical application of benzydamine solution
- Consider use of midline radiation blocks/ 3-D radiotherapy treatment
- Do NOT use acyclovir for mucositis prevention
- Do NOT use chlorhexidine, sucralfate, acyclovir, or antimicrobial lozenges to prevent mucositis

Use Intensified Mouth Care Plan: (Table 6.2)

- Drink plenty of fluids (2L/day)
- Oral Fluconazole for prevention of candidiasis

Follow oral care Recommendations of Dentist

- Dentist may order Chlorhexidine for dental caries prevention when there is no mucositis

Patient Education on mouth care and how to manage oral complications from cancer therapy

MANAGEMENT

Stepped Approach for Management

1. Mucosal coating agent (i.e. attapulgite [Kaopectate™] antacid suspensions)
   - **Do NOT use Chlorhexidine** if there is mucositis
2. Water-soluble lubricating agents (e.g. artificial saliva, KY Jelly, OraBase)
3. Topical analgesic (i.e. benzydamine)
4. Topical anesthetics (e.g. lidocaine)
   - May use Pain Relief Mouthwash if needed for oral pain (Table 7.4)
5. Systemic opioid analgesics (oral, IV bolus morphine or hydromorphone) for severe pain

Xerostomia Management for Head & Neck Radiotherapy Patients:

- Frequent sips of water
- Ice chips
- Oral pilocarpine (5mg BID to TID)
- Artificial saliva, as tolerated

Oral Hemorrhage:

- Treat with ice water and local pressure

Oral Infection

- Use appropriate antibiotic
  - For candida use oral Fluconazole (or another azole antifungal agent) for prevention or treatment
  - If Nystatin suspension used for treatment, give this after topical analgesic or anesthetic for treatment of oral fungal infection- Swish and swallow
- See Table 7.6

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Figure 7.4 Prevention & Management of Oral Complications in Hematopoietic Stem Cell Transplant (High Risk) Patients

SCREENING

Assess each patient with Mouth Care Record from beginning of treatment until all symptoms are resolved (no longer a focus of care)

Comprehensive dental exam before treatment

- Prosthodontic care prior to radiotherapy to oral cavity (i.e. TBI patients)
- Eliminate oral disease before treatment (e.g. dental extraction of high-risk dentition)

PREVENTION

Prevention- Stem Cell Transplant Patients

- Oral cryotherapy (ice chips) for 30 minutes beginning 5 minutes prior to high dose Melphalan chemotherapy (if this is part of the HSCT conditioning regimen)
- Palifermin 60 mcg/Kg daily for 3 days prior to and 3 days following stem cell transplantation (when available in Canada)
- Do NOT use pentoxyfylline or acyclovir to prevent mucositis

Use Intensified Mouth Care Plan: (Table 6.2)

- Drink plenty of fluids (2L/day)
- Oral Fluconazole for prevention of candidiasis

Follow oral care Recommendations of Dentist

- Dentist may order Chlorhexidine for dental caries prevention when there is no mucositis

Patient Education on mouth care and how to manage oral complications from cancer therapy

MANAGEMENT

Stepped Approach for Management

1. Mucosal coating agent (i.e. attapulgite [Kaopectate™] antacid suspensions)
   - **Do NOT use Chlorhexidine** if there is mucositis
2. Water-soluble lubricating agents (e.g. artificial saliva, KY Jelly, OraBase)
3. Topical analgesic (benzydamine)
4. Topical anesthetics (i.e. lidocaine)
   - May use Pain Relief Mouthwash if needed for oral pain (Table 7.4)
5. Systemic opioid analgesics (oral, IV bolus, continuous IV infusion or PCA morphine or hydromorphone) for severe pain

Oral Hemorrhage:

- Treat with ice water and local pressure

Oral Infection

- Use appropriate antibiotic
  - For candida may use oral Fluconazole for prevention or treatment
  - If oral azole antifungals are contraindicated, Nystatin suspension may be used for treatment, give this at least 30 minutes after topical analgesic or anesthetic for treatment of oral fungal infection- Swish and swallow
- See Table 7.6

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7.2.2 Management of Mucositis Symptoms

Best Practice Statement:

Patients with oral mucositis require appropriate therapeutic intervention(s) to manage the symptoms and prevent symptom progression. It is suggested to use the "stepped" approach for mucositis management, adding agents as symptoms present.

If patients develop oral mucositis, they will require appropriate therapeutic intervention(s) to manage the symptoms and prevent symptom progression. Once mucositis has developed, its severity and the degree of myelosuppression govern appropriate oral management.

Meticulous oral hygiene and treatment of symptoms are essential. A stepped approach may be used, with progression from one level to the next as follows:

1. Mucosal coating agents (e.g., antacid solutions, kaolin solutions)- to provide a temporary physical barrier
2. Water-soluble lubricating agents, including artificial saliva for xerostomia- to moisten the mucosa (Note. Oral Pilocarpine may also be indicated to stimulate residual salivary function after radiation therapy)
3. Topical analgesics (e.g. benzydamine (Tantum™) solution- to reduce pain by anti-inflammatory effect)
4. Topical anesthetics (e.g., viscous lidocaine, benzocaine sprays/gels, diphenhydramine solutions)- to reduce pain by numbing the mouth
   - In common practice, therapeutic (anesthetic) mouthwashes (section 7.4.2) are often added to the mouth care regimen when the oral mucosa becomes painful.
5. Systemic analgesics for severe pain
6. Cellulose film-forming agents for covering localized ulcerative lesions (e.g., hydroxylpropyl cellulose)- to provide a more permanent barrier for severe mucositis

Products used for the "stepped" approach, and other agents used for management of mucositis are listed in Table 7.2. It may be better to manage mucositis using the "stepped" approach than to begin with a compounded therapeutic mouthwash, holding the topical anesthetic until there is pain.

7.2.3.2 Chlorhexidine

Guideline Recommendation:

*Chlorhexidine should **not** be used to treat established oral mucositis.*

Level of Evidence: II

Grade of Recommendation: A

7.2.3.2 Management of Severe Mucositis Symptoms

Oral mucositis may be much more severe for high-risk treatment patients, and they may be admitted to hospital for management of pain and other toxicities. If oral mucositis becomes severe, there is an increased risk of aspiration of saliva. To prevent aspiration, a simple precaution is to raise the head of the bed to at least 30 degrees. Keep an emergency airway at the bedside. Keep tonsil suction at the bedside for suctioning saliva, if the patient is unable to swallow easily (if patient is not thrombocytopenic or neutropenic). If unable to use suction, put the patient on their side so that saliva can drain out of the mouth. Ensure adequate humidity. Involve respiratory experts as soon as possible.

7.3 Xerostomia

7.3.1 Salivary Gland Dysfunction and Xerostomia

The mouth is lubricated by exocrine secretions from the major salivary glands (the parotid, submandibular and sublingual glands) together with secretions from numerous smaller glands spread over the surface of the palate and tongue, and inside the lips. The smaller glands secrete saliva in response to local mechanical stimuli and, unlike the major glands, are not under parasympathetic control. The major glands are stimulated by a conditioned reflex fired by the thought, sight or smell of food. Saliva contains two major secretions- a serous fluid, containing bacteriocidal components (e.g.thiocyanate), proteolytic enzymes (e.g.lysosyme) and antibodies, notably IgA, together with alpha-amylase, an enzyme acting on starch; and mucus, which functions as a lubricant.

Saliva is important for maintaining oral health and function. It dilutes food, lubricates the oral cavity, buffers and dilutes acids produced by fermentation and continuously washes food particles and organisms from the oral cavity. When salivary function is reduced or even destroyed, the quantity of saliva is decreased and its chemical composition altered.[64-67] The saliva becomes viscous losing its lubricating qualities. It adheres to the membranes and teeth and the mouth becomes dehydrated.

Xerostomia, which is caused by changes in the salivary glands, is the subjective sensation of dryness in the mouth. [68,69] It may cause an oral burning sensation, ulceration, or soreness. The corners of the mouth can become fissured, and the tongue may become red and smooth. These consequences are due to both the diminished lubrication and the lack of saliva barrier. Discomfort, difficulty in swallowing, mastication and speaking, loss or alteration of taste sensation, may lead to anorexia, loss of weight, and cachexia.

Xerostomia promotes the accumulation of bacteria, plaque, and materia alba, which increases the patient susceptibility to caries and periodontal disease. Xerostomia is one of the most frequent side effects of cancer therapy.[70] It results from inflammatory and degenerative effects of ionizing radiation on salivary gland parenchyma, especially serous acinar cells. Salivary flow decreases within 1 week after starting radiation treatment and diminishes progressively with continued treatment. The degree of dysfunction is related to the radiation dose and volume of glandular tissue in the radiation field. Parotid glands may be more susceptible to radiation effects than submandibular, sublingual, and other minor salivary glandular tissues. Salivary gland tissues that have been excluded from the radiation portal may become hyperplastic, partially compensating for the nonfunctional glands at other oral sites.

Cancer chemotherapy can cause changes in salivation, but the changes are usually much less severe and only transient. Although only a small number of chemotherapeutic agents cause xerostomia (doxorubicin in particular), its effect may be devastating when it occurs in conjunction with existing mucositis.

Some psychotropic and sedative drugs induce xerostomia through parasympatolytic effects. Treatment with antidepressants and phenothiazines, for example, has been associated with xerostomia complicated by oral moniliasis.[71]

Table 7.3 Management of the Xerostomic Patient [76]	
Plaque Removal	Tooth Brushing Flossing Other Oral Hygiene Aids
Remineralization	Topical High Concentration Fluorides Children: Topical and Systemic Adults: Topical Remineralizing Solutions
Antimicrobials	Chlorhexidine Solutions (rinses) Povidone Iodine Oral Rinses Tetracycline Oral Rinses
Sialogogues	Pilocarpine Bethanechol Antholetrithione (Sialor™)

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7.3.2 Xerostomia Management

Guideline Statement: *Patients at risk of xerostomia may be managed by preventative measures. If xerostomia occurs in patients receiving radiotherapy to the head and neck, oral pilocarpine should be considered for systemic therapy. If the xerostomia is caused by chemotherapy or other toxic stimuli, oral pilocarpine may be considered. Artificial saliva products may also be considered, for a brief course to determine effectiveness and patient acceptability, followed by continuing therapy when warranted.*

Xerostomia may be temporarily relieved by rinsing with a mouth rinsing solution (e.g. normal saline) or by using an artificial saliva substitute. [72,73] These solutions are helpful in keeping the oral mucosa moist and free of debris and in thining secretions. Frequent sips of water, and the use of an air humidifier may also help to minimize dry oral mucosa.

On the basis of clinical practice, Krishnasamy[74] recommended sucking or chewing small pieces of fresh pineapple cubes, sugar-free chewing gum, jelly, hard candies or popsicles for the treatment of a dry mouth in advanced cancer. These recommendations are in line with those of Regnard et al.,[75] who supported the use of semifrozen tonic water and gin, semifrozen juice, frequent sips of cold water, or sprays and petroleum jelly. No scientific rationale is given for these recommendations, but most are reasonable strategies. it may also help to eat puddings or foods with sauces and gravies. Patients should **avoid tobacco and alcohol** (e.g. gin) because of their potential to dry and irritate the oral mucosa.

Patients who experience xerostomia should maintain excellent oral hygiene to minimize risk for oral lesions. Periodontal disease can be accelerated and caries can become rampant unless preventive measures are instituted. Multiple preventive strategies should be considered (Table 7.3); an example of a protocol is listed below.

- Perform systematic oral hygiene at least 4 times per day (after meals and before retiring at night).
- Use a fluoridated toothpaste when brushing.
- Apply a prescription-strength fluoride gel daily at bedtime to cleaned teeth (fluoride is ineffective on plaque-coated teeth).
- If provided through the dentist, a

custom fitted flouride tray may be used.
- Avoid foods and liquids with a high sugar content.

7.3.3 Saliva substitutes

The discomfort of xerostomia may be treated by indirect and simple measures, using saliva substitutes, for example. The use of saliva substitute before meals and conversations may help to reduce the embarrassment caused by associated speech and eating problems.

These artificial substances physically resemble saliva but do not provide the antibacterial and immunological protection of saliva.[76]

"Artificial" salivas can maintain oral comfort and may be used as often as necessary. The volume used should be the minimum needed to maintain internal lubrication; excessive quantities simply serve to enhance discomfort. One to two millilitres will often maintain lubrication up to 12 hours.

Artificial salivas usually are not associated with systemic side effects.[77] These products' effects are of limited duration, may have an unpleasant taste, may irritate the mucosa and are expensive.

Artificial salivas [78] most commonly prescribed are based on either mucin or carboxymethylcellulose.[79] Mucin-based artificial salivas are reported to be better tolerated, because mucin is a natural component of saliva.[77]

Lemon and glycerine have been recommended historically as saliva substitutes.[80] Lemon juice increases salivation, and glycerine absorbs water, so their combination actually acts to dry the mouth.[81] Although their use offers initial stimulation of saliva, this quickly results in reflex exhaustion.[82] They demonstrate no mechanical or cleaning properties, and they also attack enamel and decalcify teeth.[83]

7.3.4.4 Saliva stimulants

Guideline Recommendation: *Patients with radiation-induced xerostomia should be considered for treatment with oral pilocarpine.*

Level of Evidence: II

Grade of Recommendation: B[84]

Saliva stimulants can be used to reduce the discomfort of xerostomia. These agents fall into two categories:

1) Agents which stimulate the proprioceptive receptors within and around the oral cavity (eg, organic acids or chewing gum),
2) Agents which act directly on parasympathetic nerves (eg, pilocarpine)[83]

Saliva stimulants include citric acid [78]; malic acid, which occurs in fruit or vitamin C which is often used in palliative care settings,[78] although little evidence exists to support its use.[75,78]

Pilocarpine is the only drug approved for use as a sialogogue (5 mg tablets of pilocarpine hydrochloride). It is a parasympathomimetic agent used as a systemic agent to stimulate remaining salivary gland function in patients following radiation therapy. A number of studies have supported its use in the treatment of both non-radiation- and radiation-induced xerostomia.[80-85] The response to pilocarpine appears to be better for non-radiation-induced xerostomia, in which its action is almost always immediate,[81] It may take as long as 12 weeks to detect a response in radiation-induced xerostomia.[82] As compared with artificial saliva, pilocarpine is found to be more effective in patients with radiation-induced xerostomia.[86]

Treatment is initiated at 5 mg orally, 3 times daily; dose is then titrated up to 10 mg TID to achieve optimal clinical response and minimize adverse effects. Some patients may experience increased benefit at higher daily doses; however, incidence of adverse effects increases proportionally with dose. The patient's evening dose may be increased to 10 mg within 1 week after starting pilocarpine. Subsequently, morning and afternoon doses may also be increased to a maximum 10 mg/dose (30 mg/day).

Patient tolerance of the side effects is improved by allowing 7 days between increments. Side effects are associated with generalized parasympathetic stimulation such as sweating, headache, increased lacrimation, rhinorrhea, bradycardia, hypertension and urinary frequency, and incidence appears to be dose-related. Sweating is the most common side effect, and the most frequent reason given for discontinuing treatment.

Pilocarpine usually increases salivary flow within 30 minutes after ingestion. Maximal response may occur only after continual use. Pilocarpine may exert a radioprotective effect on salivary glands if given during radiation therapy to the head and neck.

Another agent used to treat xerostomia is antholetrithione. Antholetrithione, a sialogogue, may act directly on the secretory cells of the salivary glands, resulting in increased salivary secretion.

Interestingly, studies considering patient preference in relation to saliva substitutes and stimulants have established that patients prefer saliva stimulants.[87,88]

7.4 Oral Pain

Many oral complications are associated with pain, both local and systemic. The underlying mechanisms of mucositis (see Part 2.2) include ulceration, inflammation and the release of various cytokines, all of which are associated with local pain. In addition, pain may also be associated with the cancer. Pain can be a serious impediment to proper mouth care, eating and drinking, and quality of life for the patient. Pain sensations may range from mild to severe, with debilitating pain in many patients who receive bone marrow/stem cell transplantation procedures or radiation therapy to the head and neck.

Pain management may be local, systemic, or both. Severe pain may require parenteral opioid therapy during the maximum period of mouth pain. Pain may be managed by the use of topical analgesics to reduce somatic pain, or topical anesthetics to numb the painful tissues. Other patients require less strong measures. In addition to mucositis, pain is exacerbated by oral infections, xerostomia or pre-existing oral disease. Management of the infection or other co-morbid condition may reduce pain for many patients.

Oral pain may be associated with malnutrition. Patients are usually unwilling or unable to eat or drink when they have severe mouth pain. Nutrition deficits can further exacerbate oral complications and result in a series of problems, which further compound each other.

7.4.1 Oral Pain Management

Best Practice Statement:

Patients who experience oral pain, alone or in combination with other oral complications, may be treated with coating suspensions, topical analgesic solutions, topical anesthetics or pain relief mouthwash suspensions, and systemic

analgesics (for increasing severity of the pain). Clinicians should only use the institutional standard(s) for pain relief mouthwash formulations.

For patients with localized areas of oral pain, focal application of a topical anesthetic agent is preferred. If the pain is throughout the oral cavity, the patient may require more widespread application. These agents have a 5-minute onset of action and a duration of less than one hour. Products such as 2% viscous lidocaine, diphenhydramine solution may be absorbed systemically and cause adverse side effects including hypertension, hypotension, bradycardia, tachycardia, electrocardiographic changes, and central nervous system depression.

Some commercial products are used as topical analgesics (e.g. benzydamine solution[89-91]) or topical anesthetics (e.g. diphenhydramine suspension). These may reduce inflammation or cause mild numbing effect, without suppression of the gag reflex.

Many extemporaneously prepared mixtures incorporate a coating agent such as milk of magnesia, attapulgite (kaolin with pectin) suspension, mixtures of aluminum, and/or magnesium hydroxide suspensions (many antacids) combined with a topical anesthetic agent to provide relief. (See Pain Relief Mouthwashes, Part 7.4.2). The choice of coating agent should take into consideration the laxative or constipating effects of different antacids. The purpose of a combined product is to simplify administration when multiple agents are needed in the 'stepped approach' for managing oral stomatitis symptoms (see Part 7.2.2). Other agents, such as nystatin for oral candidiasis are NOT recommended for inclusion in compounded products, for a number of reasons:

- Topical non-absorbable antifungals (e.g. Nystatin) are not effective for prevention and less effective than oral absorbable antifungals (e.g. fluconazole) for treatment of candidiasis
- The mucositis symptoms may not occur over the same time interval as any oral infection
- Addition of several agents may result in an unstable compound
- Usually, it is important to manage the oral pain before any other product is used in the mouth, so analgesia or anesthesia should be achieved first. Then the nystatin suspension may be held in the oral cavity for a longer exposure time and swallowed to coat the entire throat (anesthetic compounds must be spit out- not swallowed)

Mixtures of topical anesthetics, analgesic agents, and antacids also are used to decrease oral pain and discomfort. Systemic nonsteroidal anti-inflammatory drugs that effect platelet adhesion and damage gastric mucosa should not be used if thrombocytopenia is present.

Capsaicin preparations may be effective in controlling oral mucositis pain.[92-95] Capsaicin and its analogues are the active ingredients in chili peppers that produce burning pain by stimulating polymodal nociceptors, the predominant pain receptors found in skin and mucous membranes. It has been demonstrated experimentally that after ingesting capsaicin-containing foods or after capsaicin application to the oral mucosa, severity of pain is directly proportional to concentration of capsaicin present. Capsaicin's clinical potential derives from the fact that it elevates the threshold for pain in areas to which it is applied. The pain threshold can be further elevated

Table 7.4 Pain Relief Mouthwash Formulations [99]

Pain Relief Mouthwash with Attapulgite (Kaopectate™) Mild constipating effect

• Diphenhydramine 6.25mg/5 mL (Benadryl™) liquid	50 mL
• Lidocaine (Xylocaine™) viscous 2%	25 mL
• Attapulgite (Kaopectate™) suspension	25 mL
TOTAL VOLUME	100 mL

- After brushing teeth and rinsing mouth, swish 10-15mL for up to 2 minutes, then spit out or swallow slowly. Repeat TID-QID PRN. Avoid putting anything in the mouth (including medications) for 30 minutes, especially if mouthwash swallowed.
- Lidocaine may inhibit gag reflex. Systemic absorption of swallowed lidocaine may be contraindicated in patients with impaired cardiovascular function. Do not give more than 6 times daily. If this is a problem, order Pain Relief without Lidocaine.
- Duration of action of lidocaine about 30-60 minutes.
- In Capital Health: If the order reads "Magic Mouthwash", Pharmacy will automatically substitute Pain Relief Mouthwash with Attapulgite.

Pain Relief Mouthwash with Antacid Balanced effect on the bowels

• Diphenhydramine 6.25mg/5 mL (Benadryl™) liquid	50 mL
• Lidocaine (Xylocaine™) viscous 2%	25 mL
• Magnesia-Alumina Concentrate Suspension (Maalox TC™)	75 mL
TOTAL VOLUME	150 mL

- After brushing teeth and rinsing mouth, swish 10-15mL for up to 2 minutes, then spit out or swallow slowly. Repeat TID-QID PRN. Avoid putting anything in the mouth (including medications) for 30 minutes, especially if mouthwash swallowed.
- Lidocaine may inhibit gag reflex. Systemic absorption of swallowed lidocaine may be contraindicated in patients with impaired cardiovascular function. Do not give more than 6 times daily. If this is a problem, order Pain Relief without Lidocaine.
- Duration of action of lidocaine about 30-60 minutes.

Pain Relief Mouthwash without Lidocaine Mild constipating effect

• Diphenhydramine 6.25mg/5 mL (Benadryl™) liquid	50 mL
• Attapulgite (Kaopectate™) suspension	50 mL
TOTAL VOLUME	100 mL

- After brushing teeth and rinsing mouth, swish 10-15 mL for 2 minutes, then swallow. Repeat TID-QID PRN. Do not put anything (except water) in the mouth for 30 minutes after treatment.
- Administer Pain Relief Mouthwash before any other medications and wait 30 minutes before administering.
- Used for patients who cannot tolerate lidocaine anesthetic.
- Diphenhydramine may cause sensitization of the oral tissues.

NOTE: Oral fluconazole is recommended as first choice for prevention or treatment of oral candidiasis. Mouthwash formulations that include Nystatin suspension are not covered by public prescription insurance plans (e.g. Pharmacare). If oral azole antifungal agents are contraindicated and Nystatin is needed for oral candidiasis, it may be given 30 minutes AFTER the appropriate Pain Relief Mouthwash has been used, both to reduce pain from active swishing of Nystatin around the mouth, and to allow the Nystatin to be swallowed (to coat the back of the throat)

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by gradually increasing the capsaicin concentration in a series of repeated applications. This approach to mucositis pain control is not convenient and some patients are clearly not candidates for its use. Thus far, evidence that capsaicin produces symptomatic relief for mucositis pain is encouraging but limited to anecdotal reports and a small case series. It is not yet known what effects capsaicin may have on compromised human gastrointestinal mucosa at doses and durations that may be useful in treating mucositis. Further evaluation is warranted.

Pain associated with clenching or bruxism (i.e. grinding the teeth) may be eliminated by calling it to the attention of the patient and by the use of a bite guard fabricated by a dental professional.

7.4.2 Pain Relief Mouthwashes

Best Practice Statement:

An analgesic or anesthetic mouthwash should be considered for management of patients with oral pain. For ease of administration, multiple components may be compounded together into a pain relief mouthwash preparation. The appropriate compounded mouthwash preparation should be incorporated into the oral care procedures.

Compounded preparations should not include more than one agent from the same therapeutic classification. An institution should limit the selection of compounded pain relief mouthwash preparations to two or three standard formulae.

In many institutions, a variety of empiric preparations have been formulated to prevent and/or treat symptoms of stomatitis. Formulations vary, but typically include a coating agent with a topical anesthetic agent[96-98]. Mucosal coating agents may help to thicken the formulation so that anaesthetic agents adhere more effectively to mucous membranes. They also improve palatability.

Since each prescriber may have unique personal preferences, the number of formulations may become confusing at institutions with major oncology programs. Many of these formulations are euphemistically titled as "Magic Mouthwash", "Miracle Mouthwash" or similar names. It is not uncommon to have several "Magic Mouthwash" formulations on record at the same time, leading to confusion by many health care professionals. Often the empiric formulation may include Nystatin, other antibiotics or other ingredients. These agents are not recommended for mucositis prevention (Section 7.2.1.5) or infection prophylaxis (Section 7.5.1), so these agents should not be included in mouthwash formulations.

To eliminate the potential confusion, it is advised for institutions to limit the number of formulations, and to use descriptive names rather than fanciful titles. Formulations should not contain more than one drug from the same therapeutic classification, and should keep the ingredient list to the minimum of items specifically needed to manage oral stomatitis and pain.

At the QEII Health Sciences Centre, 3 standard formulations have been developed for pain relief mouthwashes.[99] Additional formulations are discouraged, to avoid excessive formulation complications and confusion. The standard formulations are described in Table 7.4.

7.4.3 Management of Severe Oral Pain

Guideline Recommendation:

Hematopoietic stem cell transplant (HSCT) patients should be offered patient-controlled analgesia with morphine (or other strong opiate) to manage severe oral pain.

Level of Evidence: I

Grade of Recommendation: A

Systemic analgesics such as acetaminophen and codeine may be administered when topical anesthetic strategies are not sufficient for clinical relief. Acetaminophen elixir can be swished in the mouth and then swallowed for local and systemic relief of pain. Oral medications should be administered 60 to 90 minutes before meals to maximize pain relief. When pain is severe, opioids may be needed. Opiates such as morphine have been effective in relieving severe and transient pain associated with oral complications.[100] The combination of tunnelled indwelling venous catheters and computerized drug administration pumps to provide patient-controlled analgesia (PCA) has significantly increased the effectiveness of controlling severe mucositis pain while lowering the dose and side effects of opioid analgesics (see Appendix IV).[101] For some patient populations, where there is intense oral pain for a relatively short period of time, and the patients are dealing with a variety of complex care needs (i.e. hematopoietic stem cell transplant), it may be more appropriate to provide continuous intravenous or subcutaneous infusion of opioid.

7.5 Oral Infection [102-106]

Following cytotoxic therapy, the pathogenicity of the oral flora is likely to increase. Generally, more intense cytotoxic therapy is associated with more common oral infection complications.[107-109] Infections of the oral cavity may arise from previous commensal organisms or from introduced pathogens. The major pathogens involved in infections occurring in the mouth include gram-negative bacteria, candida and herpes viruses. These organisms acquire the ability to cause both oral and systemic infection because of disruptions of the skin and mucosa.[109]

Factors that influence the initiation, development, and severity of an infection include the host's primary physical barriers against invasions, the ability of the organism to destroy the host's defenses[110], the manner in which the organisms spread and causes disease, and the ability of the body to control and eliminate invading organisms. Adherence to a prospective mouth care plan (see below) is believed to reduce the potential for infections in the oral cavity.

Neutrophils are an important factor associated with infection in the immunocompromised patient and act as the body's first line of defense once microbial invasion has occurred. In patients with cancer, the signs and symptoms of infection may be less pronounced if the patient is neutropenic.

Factors increasing the risk of infection in cancer patients

- Intrinsic immune deficiencies
- Malignancy-induced hemopoietic and immune deficiencies
- Chemotherapy-induced myelosuppression or immunosuppression
- Other immunosuppressant drugs (e.g. prednisone)
- Obstruction of the lymphatic system
- Drug therapy which encourages growth of resistant pathogens
- Tumour necrosis
- Generalized physical debilitation

- Nosocomial infection
- Inadequate hygiene
- Nutritional deficiency

7.5.1 Infection Prevention

Best Practice Statement:

Treatment with prophylactic antibiotic therapy may be considered for patients who are seriously myelosuppressed and/or who have poor oral hygiene, to prevent oral infections. Antibiotic prophylaxis may be topical or systemic.

*Prophylactic use of chlorhexidine to prevent serious oral infections is not recommended for adults. Potential antimicrobial effects are offset by other adverse effects in patients with oral mucositis. Chlorhexidine **may** be used for prevention of dental caries and plaque, but **should not** be used during symptomatic episodes of mucositis.*

7.5.1.1 Chlorhexidine

Despite early enthusiasm for the use of chlorhexidine as prevention or treatment of oral mucositis, subsequent clinical trials failed to support initial observations. The detrimental effects of chlorhexidine in treating radiation-induced mucositis, are exacerbation of pain and irritation as a result of its astringency. Chlorhexidine is NOT recommended for prevention or treatment of mucositis in adults (see section 7.2.1.5).[117] Evidence is lacking to support a recommendation to use chlorhexidine specifically for antimicrobial prophylaxis.

Chlorhexidine is a quaternary ammonium compound with topical antimicrobial properties. Chlorhexidine gluconate 0.12% oral rinse may be used alone or in conjunction with other prophylactic topical and systemic antibiotics in the high-risk patient populations. Several studies have found products containing chlorhexidine[111-115] to have antibacterial effects,[116] which may exert an antibacterial effect for as long as 12 hours.[116] Chlorhexidene is effective against gram-positive and gram-negative infections, yeast, and fungi, and it prevents dental plaque formation. It also has the desirable properties of sustained binding to oral surfaces and minimal gastrointestinal absorption, thereby limiting adverse systemic effects.

Chlorhexidine has been successfully included in oral care plans for several years. Chlorhexidine is not well tolerated by many patients, however, with an unpleasant taste due to an alcohol content of 9.6%.[112] Chlorhexidine can cause burning and stinging. Brown staining of the teeth occurs commonly but can be removed with oxidizing agents.[116] Chlorhexidine oral rinse may be used as a mouthwash and gargle, but should not be ingested. Chlorhexidine may exacerbate mouth pain and irritation when used to treat radiation-induced mucositis.

For children, the Atlantic Provinces Pediatric Hematology/Oncology Network (APPHON)[119] recommends the use of an alcohol-free chlorhexidine solution as a standard antibacterial mouth rinse for pediatric patients receiving cancer treatment[118]. However, the use of some commercial preparations (e.g. Peridex™,

Table 7.5 Chlorhexidine Mouth Rinse for Pediatric Oncology Patients

Age	Volume of Mouth Rinse	Interval Options
< 6 years	5 mL	Swab mouth or rinse soother or swish and spit out up to QID
> 6 years	10 mL	Swab mouth or swish and spit out up to QID

Table 7.6 Presentation and Treatment of Oral Infections in Cancer Patients

Oral Infection	Appearance and Characteristics	Treatment

Fungal infections including	**Candidiasis**
	Oral candidiasis may have one of several different clinical appearances
	• Pseudomembranous candidiasis, also known as thrush, is the most common form of oral candidiasis. It typically appears as white patches on the surface of the oral mucosa, and/or tongue, that develop into confluent plaques that resemble milk curds and can be wiped off to reveal a raw erythematous and sometimes bleeding base which may be tender.
	• Chronic hyperplastic candidiasis (or candidal leukoplakia) is a less common, asymptomatic form of candidiasis, that appears as a dense, white plaque that is hard and rough to the touch (plaquelike lesion). Homogeneous or speckled areas, which do not rub off (nodular lesions), can be seen, usually on the inside surface of one or both cheeks.
	• Angular cheilitis (perleche) is a type of candidiasis that appears as red, eroded, fissured lesions which occur bilaterally in the commissures of the lips and are frequently irritated and painful.
		Systemic antifungals are usually the drug of choice for prevention and/or treatment of candidiasis in patients with normal immune function.
		• **Fluconazole 100 mg** daily is equal or more effective against oropharyngeal candidiasis in cancer patients than nystatin or clotrimazole. Prophylactic fluconazole 100 mg PO daily (400 mg PO daily for HSCT patients) may be considered for prevention of oral candidiasis in cancer patients. Maintenance therapy to prevent relapse after initial treatment- 50 mg (up to 400 mg) daily.
		• **Nystatin** suspension 100,000U/mL- Use in patients who cannot tolerate Fluconazole (or other azole antifungals); Swish around and hold in the mouth for at least one minute, then swallow; use 5 mL qid for 7-14 days (works by direct contact)
		  • For children, use 2mL for infants, or 4 to 6 mL for children- Swish and swallow or swab mouth QID
		• Nystatin cream to treat dentures
		• Nystatin popsicles (for cooling relief)
		• **Clotrimazole** oral suspension 1mg/mL- Swish around the mouth for one minute and then swallow; use 10 mL qid
		  • For children, use 3mL if < 1 year, 5mL if 1-3 years, , or 10mL if > 3 years- Swish and swallow or swab mouth
		• Clotrimazole troche 10 mg 5 times per day

Bacterial infection	Periodontitis or gingivitis (oral infections) usually appear as reddened gums which bleed easily on probing. When the natural flora is affected by cancer therapy, some of the bacteria may proliferate and invade the gastrointestinal, cardiovascular, renal, or respiratory systems, resulting in systemic infections (such as bacterial endocarditis or glomerulonephritis). Local infections in the oral cavity may provide foci for systemic infection.	Eliminate oral sources of bacteremia before chemotherapy (consult dentist) • Assessment and interventions for advanced periodontal disease, periapical pathosis **Broad-spectrum systemic antibiotic** therapy (e.g. Cloxacillin or cephalexin)

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Table 7.6 Presentation and Treatment of Oral Infections in Cancer Patients (continued)		
Oral Infection	**Appearance and Characteristics**	**Treatment**
Herpes simplex	Symptomatic primary infection, with multiple, small, clustered vesicles in numerous locations, can occur anywhere in the oral cavity, on the perioral skin, on the lips, or on the pharynx, and can be severe. Extensive ulceration can make eating painful. Headache, fever, painful lymphadenopathy, and malaise are common. Recurrent herpes lesions (or cold sores) occur on keratinized mucosa (usually the lips, attached gingiva, and/or the hard palate). Vesicles often break quickly, so the lesions may appear as small clustered ulcers.	**Topical acyclovir**- Apply to affected area q3-4h, for a total of 6 times/d, for 7 d; apply a sufficient quantity to adequately cover all lesions **Systemic acyclovir** for larger lesions • Primary HSV: 200 mg q4h PO 5 times/day for 10 days or 500 mg tid PO for 7-10 days (In immunocompromised patients, consider 400 mg q4h PO 5 times/day for 10 days) • Recurrent HSV: 200 mg q4h PO 5 times/d for 5 d **Valacyclovir** 500 mg BID PO
Varicella-zoster	Recurrent varicella (also known as herpes zoster or shingles) results in a vesicular rash that usually affects a single dermatome. Inside the oral cavity, this may be observed as vesicles or ulcerations that stop sharply at the midline. A prodrome of pain, burning, or itching that mimics a toothache may occur. After the resolution of the rash, postherpetic neuralgia may linger for a month or longer, especially in patients who are immunosuppressed.	**Acyclovir** 400 mg 5 times/day PO for 7-10 days; for severe infection, 5 mg (base) per kg body weight q8h IV for 5-7 days (administer over at least 1 h); patients with acute or chronic renal impairment may require dose reduction (200 mg q12h PO when CrCl 0-10 mL/min) **Valacyclovir** 1000 mg TID PO for 7 days (superior to acyclovir for post-herpetic infections)
Cytomegalovirus	CMV infection may cause esophagitis, which is occasionally accompanied by oral ulcerations or erythema. Oral ulcerations are clinically nonspecific; a biopsy is required for definitive diagnosis.	**Ganciclovir** (individualized dosing)
Non-herpes virus infections	Verruca vulgaris (common warts) in the oral cavity are usually sharp-tipped, verrucous, white and elevated with discrete borders. The lesions most commonly occur on the lips, hard palate, or gingiva. Verruca plana is similar but less elevated. Warts are commonly observed on the digits of patients with oral infection. Condyloma acuminata, or genital warts may also affect the oral mucosa. These lesions are usually cerebriform, pink, and sessile; they occur more commonly on non-keratinized mucosa than on keratinized mucosa.	**Laser surgery** or **cryotherapy** to remove oral HPV lesions Intralesional injections of Imiquimod (Aldara™) may be used for recurrent lesions May be surgically excised

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Pericleanse™) is not recommended, since these contain local anesthetic agents or alcohol. The mouth rinse solution is dosed as outlined in Table 7.4.

7.5.2 Infection Management

Best Practice Statement:

Treatment with appropriate antibiotic agents should be considered for patients with an active oral infection, especially in patients who are immunosuppressed. Antibiotic treatment is usually systemic, and the treatment plan should consider fungal, bacterial and viral opportunistic superinfections. If topical antibiotics are used, they must be given in conjunction with proper oral hygiene as part of the mouth care plan.

Patients with clinically-diagnosed infections should be treated with the appropriate antibiotics for the empiric or pathologically-confirmed diagnosis. Treatments are listed in Table 7.6. For patients using a number of oral medications, timing for each agent is important. As a rule, mouth cleansing should be performed first, to remove any debris. If a topical anesthetic or analgesic is required (for pain relief), this should be used next, and no further applications for about 30 minutes (until pain relief is achieved). The topical antibiotics should be applied last. Since these agents work by topical exposure, it is important to leave the mouth alone for at least 30 minutes, for maximal antibiotic effect. The patient should avoid putting anything in the mouth, including fluids, for this time. It is also important to remove any dentures or other oral prostheses before each session of mouth care, and to disinfect these devices at the same time as the mouth. The patient could otherwise re-introduce microbes after topical disinfection of the mouth.

7.5.3 Fungal infection

Guideline Recommendation[121]**:**

Patients who are at risk, or who have been diagnosed with candidiasis (thrush) should be treated with oral fluconazole 100mg qd (or another oral azole antifungal agent).

Level of Evidence: I

Grade of Recommendation: A

Best Practice Statement:

Oral nystatin suspension or alternate forms of nystatin delivery may be considered if fluconazole (and other azole antifungal agents) is contraindicated.

Fungi can exist in the oral mucosa when the integrity of the mucosa is uninterupted and protected by rapid cellular renewal. Disruption in the integumentary and mucosal barrier, disease, and immunosupression can lead to invasive fungal infections. *Candida albicans*, which is part of the normal gastrointestinal and oral flora in 20 to 50% of the population, is the primary cause of opportunistic fungal disease in patients who are immuno-compromised. In healthy subjects, candida is typically present as a blastopore; when pathogenic, it can also exist in a hyphal form.

Under normal conditions, its growth is inhibited by other microorganisms (*Lactilobacillus acidophilus*, in particular) and by an intact immune system. However, in cancer patients, humoral and cell-mediated immunity, the lines of defense against this infectious organism, are depieted.[120] There is evidence to support prophylatic antifungal treatment for HSCT patients, however prophylaxis is suggested for all patients at high risk of mucositis and may be considered for intermediate mucositis risk patients.

7.5.3.1 Candidiasis

A candida infection is often characterized by white, curd-like elevations with a peripheral zone of erythema over an inflamed mucosa. There are other clinical presentations. Overgrowth of candida causes several types of lesions, including pseudomembranous candidiasis (removable white plaques), chronic hyperplastic candidiasis (leukoplekia-like white plaques that do not rub off), and chronic erythematous candidiasis (patchy or diffuse mucosal erythema). The variable presentation of this infection may complicate diagnosis.

The tongue, mucosa, and commissures of the lips are most frequently affected. Once established, *C albicans* may spread to the esophagus or lungs via deglutition or droplet aspiration, or through the hematologic route, and all organs systems may be affected. Oral candidiasis can occasionally be refractory to treatment and potentially lethal.

Azole Antifungals

There is clear evidence that prophylactic systemic azole antifungals can effectively reduce overall oral fungal colonization levels and reduce the risk of oral candidiasis, with fluconazole being the agent of choice.[121-126] Fluconazole has been studied in a range of doses, from 50 mg to 400 mg daily in adults (or 6 mg/Kg loading dose, then 3 mg/Kg for 2 weeks in children). **The indicated dose in adults is 100 mg PO daily.** Higher doses (400 mf PO daily) are used for prophylaxis during HSCT and for immunocompromised patients. The drug is available as oral capsules, oral suspension and injectible solution. Serious adverse effects include some cardiac arrhythmias and hepatotoxicity; less serious adverse effects include headache, rash, nausea, diarrhea, myelosuppression and dyspnea. Azoles act by interfering with the cytochrome P 450 (CYP450) enzymes in the fungi, so Fluconazole (and other azoles) interacts with several other drugs through the human CYP450 hepatic enzyme system.

Ketoconazole is an alternative azole antifungal agent to consider[127-129], however, it is rarely used in routine clinical practice. Patients on ketoconazole may develop nausea and vomiting or increase in transminase levels (rarely hepatitis).[108,136]

Clotrimazole

Clotrimazole is an effective alternative antifungal agent.[122,136-140] The lozenges are taken five times a day and should be allowed to dissolve slowly in the mouth. Clotrimazole can both prevent and treat candidiasis in the oropharyngeal area and taste more pleasant if used in the same way as the nystatin suppository.

For pediatric oncology patients[119], clotrimazole extemporaneous suspension is recommended as the treatment of first choice for uncomplicated oral thrush. The IWK uses a suspension formulation with 1 mg/ mL, that may be prepared at the community pharmacy (if not available, nystatin suspension may be used). Pediatric dosing guidelines are age-based:

- Clotrimazole 3 mg/ 3 mL if < 1 year
- Clotrimazole 5 mg/ 5 mL if 1-3 years
- Clotrimazole 10 mg/ 10 mL if > 3 years

Clotrimazole (or Nystatin) suspension should be given before Chlorhexidine mouth rinse.

Side effects may be less frequent than Nystatin, with nausea and anorexia reported in 5% to 10% of cases. With prolonged use, induction of hepatic enzymes can occur, leading to reduced efficacy. This outcome may be avoided by the use of an intermittent dosing schedule.

Nystatin

Research studies utilizing topical non-absorbable oral antifungal agents appear to have variable but low efficacy in treating fungal infection in immunocompromised patients. Nystatin, in particular, has been shown to be ineffective in prevention of candidiasis[121]. The historic treatment of oral candidiasis was nystatin in the form of a vaginal suppository used as a lozenge four times daily. Prolonged contact between the medication and the infected surface increases the local effect of the medication. Nystatin suspension[130], if used, should be swished around the mouth for one minute and then swallowed. The nystatin oral suspension may be frozen in the form of ice cubes, which provide prolonged mucosal contact and taste better. The elevated sugar level contained in this product may adversely affect the teeth, and the taste is not always well accepted by patients.[131,132] Several studies have demonstrated the inability of nystatin suspension to effectively reduce incidence of either oropharyngeal or systemic Candida infections in immunocompromised patients receiving chemotherapy or radiation. Although topical antifungal prophylaxis and treatment may clear superficial oropharyngeal infections, topical agents are not well absorbed through the GI tract and are ineffective against more deeply invasive fungal infections. The practice continues in many centers.[133-135]

Amphotericin B

In carefully selected and evaluated patients in whom the risk/benefit ratio favors the use of a potential toxicity, IV amphotericin B can be used. It is the preferred drug for treating serious systemic infections[141-144]; however this medication may compromise renal and liver function, and is associated with many adverse effects.[127,145]

Administration of Topical Antifungals

Patients with superficial candidiasis should be instructed to:

1. Remove dentures so there is direct tissue contact with the medication(s).
2. Clean the oral cavity prior to administering topical antifungal medication; irrigation and plaque removal by tooth brushing may be necessary prior to drug dosing. Rinse well with rinse solution.
3. If there is pain, use the topical pain relief analgesic or anesthetic mouthwash and wait 30 minutes before using antifungal.
4. Do not rinse mouth or put anything in the mouth for 30 minutes after each dose of topical antifungal.
5. Clean and disinfect any dentures or dental prosthesis, using the same mouth rinse and topical antifungal as used in the mouth. Coat surfaces of denture and contact mouth tissues with antifungal suspension (or cream) using a sterile swab. If no topical antifungal is used, simply clean thoroughly and rinse. Store dentures or prosthesis in a fresh solution daily.
6. If xerostomia is present, use a suspension instead of a lozenge/ vaginal suppository (if a lozenge is preferred, the patient should rinse or drink water prior to dosing).

7.5.3.2 Noncandidal Fungal Infections

An increasing number of different fungal organisms are being associated with oral infection in immunocompromised cancer patients in recent years, and includes infection by species of *Aspergillus, Mucormycosis,* and *Rhizopus.*[146] The clinical presentation is not athognomonic; lesions may appear similar to other oral toxicities.

Microbiologic documentation is essential. Systemic antimicrobial therapy must be instituted promptly due to high risk for morbidity and mortality.

7.5.4 Viral infection [147,148]

Herpes group viruses can be associated with important oral disease in patients receiving cancer therapy. [149-152] In most instances, herpes simplex virus (HSV), *varicella zoster* virus (VZV), and *Epstein Barr* virus (EBV) infections result from reactivation of latent virus, while *cytomegalovirus* (CMV) infections can result from either reactivation of latent virus, or via a newly acquired virus.

Herpes simplex

Herpes simplex, a recurrent viral infection, is characterized by single or multiple clusters of small vesicles filled with clear fluid on a raised inflammatory base that appears on the skin or mucous membranes. Recurrent herpetic eruptions can be precipitated by febrile illnesses, physical or emotional stress, overexposure to sunlight, or certain foods and drugs. The lesions may appear anywhere on the mucosa, but oral lesions are seen most frequently on the lips or in the mouth. Following a short prodrom period of tingling or itching, small vesicles appear on an erythematous base. The vesicles persist for a few days, then begin to dry, forming a thin, yellowish crust, that is easily removed from the mucosa and is extremely painful. Healing begins 7-10 days after onset, with lesions varying in size from 0.5-1.5 cm. Reccurrent lesions at the same site may cause atrophy and scarring.

Patients with prior HSV infection have HSV antibodies. In the presence of immunosuppression, the latent virus can be reactivated, causing oral or disseminated infection. In patients who are immunocompromised, the mucositis associated with HSV may be more painful, severe, and prolonged. HSV ulcerations may act as portals of entry for bacterial and fungal pathogens.

Small lesions of herpes simplex may be treated with topical acyclovir. [149,150] With progressive or larger lesions, measures to prevent suprainfection and treatment with systemic acyclovir are recommended. This drug has few side effects. Patients should be well-hydrated and the dose may need to be diminished if the creatinine clearance is low. [152-155] Acyclovir reduces viral shedding, pain, and healing time. Antiviral therapy should be initiated as soon as possible following the onset of the symptoms and may be taken for 7-10 days. Care should be taken to avoid transmission of the infection to other body sites when applying the ointment. True resistance to anti-virals may develop, clinical infection is likely due to insufficient dosing or compromised gastrointestinal absorption of oral acyclovir. Topical therapy alone is generally not efficacious in the immunocompromised patient.

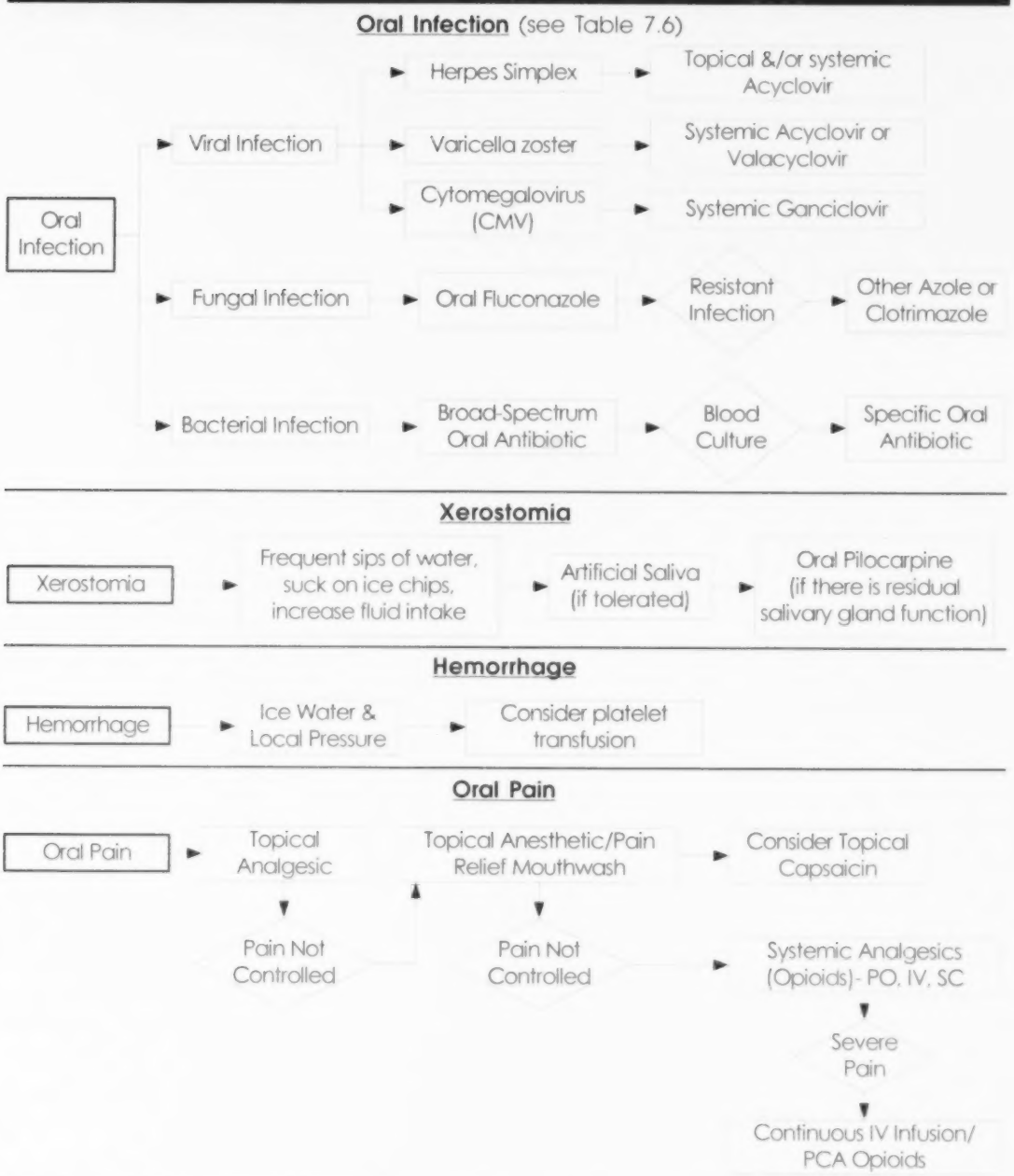
Topical, oral, and systemic acyclovir may be used prophylactically to minimize the recurrence of HSV in the patient who is severely myelosuppressed. Extraoral HSV infections characteristically become infected secondarily.

Bacitracin (neosporin) ointment helps keep viral lesions lubricated and free of secondary infections.

Herpes zoster virus

Herpes zoster [149] (or varicella zoster) is a painful, unilateral vesiculation that may follow the distribution of a branch of the trigeminal nerve. The lesions coalesce into large ulcerations and may linger for weeks before remission occurs. Recurrent infections frequently affect patients who are myelosuppresed. The lesion is typically observed several weeks after cessation of chemotherapy. This is in contrast to HSV, which often occurs within two to three weeks after chemotherapy is discontinued. Herpetic infection can give noticeable morbidity and can have a

Figure 7.5 Management of Specific Oral Complications in Cancer Patients



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chronic course. Systemic spread, which can have great consequences, is fortunately infrequent.

Acyclovir and valacyclovir are currently the primary drugs used for treatment of varicella-zoster infections. [156]

Cytomegalovirus

Oral lesions associated with Cytomegalovirus (CMV) have been documented in recent years. [157,158] Appearance is not pathognomonic and is characterized by multiple mild-moderate ulcerations with irregular margins. The lesions initially present during early periods of marrow regeneration (e.g., 3 weeks after chemotherapy is discontinued).

Ganciclovir for treatment of acute systemic CMV infection should be considered. [157,158]

Epstein-Barr Virus

Oral hairy leukoplakia has been attributed to EBV infection in immunocompromised patients. The lesion does not appear to be clinically significant in chemotherapy recipients.

Non-herpes virus infections

Infections caused by non-herpes viruses are less common in immunocompromised chemotherapy patients. Oral lesions caused by adenovirus and oral human papilloma virus (HPV) have been described.

Laser surgery, cryotherapy or surgical excision are typically utilized to remove oral HPV lesions; intralesional injections of Imiquimod (Aldara™) may prove effective for recurrent lesions. These lesions may also be surgically excised.

7.5.5 Bacterial infection

Bacterial infection may present with small hemorrhages, pain localized in the periodontum, and fever. Other signs of inflammation are often missing. Clinical presentation may vary depending on the bacterial source and immune status of the patient. Evidence of secondary infection in nearby structures may be present. These often contribute to morbidity in cancer patients, and occasionally to mortality. Bacterial infections in the mouth may originate from an odontogenic source, or in the mucosa or salivary glands.

The Gram-positive microorganisms (*staphylococci* and *streptococci*) normally inhabit the mouth but are potentially opportunistic. Gram-negative infections are also commonly seen in oral cavities of cancer patients. As a result of myelosuppression, the mouth may be inoculated by enteric Gram-negative microorganisms such as *Klebsiella, Pseudomonas* [159], *Proteus, Serratia,* and *Escherichia coli.*

Table 7.7 Strategies to Treat Oral Hemorrhage

- A sponge-tipped applicator or a piece of gauze saturated with ice water
- Applying pressure with a frozen, wet tea bag
- Irrigating the oral cavity with cold water
- Gauze soaked in topical thrombin solution (when available), applied to the affected area with pressure
- Do not remove any clots that form
- Microcrystalline collagen applied to a dry site for several minutes (see product instructions)
- Platelet transfusions may be considered for thrombocytopenic patients

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Myeloablated cancer patients with chronic periodontal disease may develop acute periodontal infections with associated systemic sequelae. Pulpal/periapical infections of dental origin can complicate the course of the chemotherapy patient. These lesions should be eliminated prior to initiation of chemotherapy.

Oral sources of bacteremia should be eliminated before onset of chemotherapy. Such sources particularly include areas of advanced periodontal disease, teeth with soft tissue coverage and periapical pathosis. Antibiotic prophylaxis must be considered before dental treatment. [160,161]

The treatment of bacterial infection depends first on adequate hygiene. In acute periodontal infection, broad-spectrum antibiotic therapy is usually initiated. Typical empiric antibiotic therapy may be penicillin (with or without metronidazole) for odontogenic infections. Clindamycin may be substituted for penicillin-allergic patients. If bacterial cultures can be obtained, the antibiotic therapy may be modified to match the bacterial sensitivity profile.

The Gram-positive microorganisms (Staphylococcus-streptococcus) are usually treated with cloxacillin or cephalexin.

Focal bacterial infections of the mouth are often suspected as the source for infections of other organs, such as the heart (bacterial endocarditis), kidneys (glomerulonephritis), gastrointestinal and respiratory systems. in addition, bacterial infections of the mouth may coexist with viral and/or fungal infections. Careful diagnosis is required whenever an oral infection is suspected or observed.

7.6 Hemorrhage

Hemorrhage may be present clinically as gingival bleeding, submucosal bleeding with hematoma formation, or disseminated intravascular coagulation (DIC). Bleeding usually results from trauma or pre-existing periodontal disease and usually is intermittent with soft, fragile clots that form and break away. The most common oral bleeding sites include the lips, tongue, and gingiva. Bleeding from the oral cavity may occur in the presence of thrombocytopenia. The potential for spontaneous bleeding exists when a patient's platelet count falls below 20×10^9/L.

Local etiological factors, such as mucositis, plaque and mucosal dryness, due to mouth breathing, oxygen therapy or varying degrees of xerostomia, may increase the hemorrhagic tendency.

7.6.1 Hemorrhage Management

Prevention is the most effective technique used to avoid hemorrhage. Eliminating potential areas of trauma (sharp restorations, fractured teeth) and pre-existing intraoral disease before chemotherapy will prevent hemorrhage. Oral care must be performed very gently to reduce risk of hemorrhage. It is important in decreasing hemorrhagic tendencies in patients with thrombocytopenia who are receiving chemotherapy.

A sponge-tipped applicator or a piece of gauze saturated with ice water may help to control bleeding. Applying pressure with a frozen, wet tea bag or irrigating the oral cavity with cold water or saline also may decrease bleeding by causing vasoconstriction.

Gauze soaked in topical thrombin solution (when available) and applied to the affected area with pressure also can help to minimize bleeding. Clots that form

should not be removed to avoid repeated bleeding. Microcrystalline collagen applied to a dry site for several minutes also may decrease hemorrhage.

Depending on the hematologic status of the patient, platelet transfusions may also be required.

7.7 Dental growth

The developing tooth, and to a lesser extent the adult tooth, both present constituent cells that exhibit proliferation, maturation, and secretion. Both the developing tooth and the mature tooth have a complex interrelationship with the supporting mandible.[162-168]

Altered dental growth and development is a frequent complication for long term cancer survivors who received high dose chemotherapy and/or head/neck radiation for childhood malignancies.[169-176] Developmental disturbances in children treated at ages less than 12 years generally affect size, shape, and eruption of teeth as well as craniofacial development. Abnormal tooth formation manifests as decreased crown size, shortened and conical shaped roots, and microdontia; on occasion, complete agenesis may occur. Eruption of teeth can be delayed, including increased frequency of impacted maxillary canines. Shortened root length is associated with diminished alveolar processes, which in turn leads to decreased occlusal vertical dimension. Additionally, conditioning-induced injury to maxillary and mandibular growth centers can compromise full maturation of the craniofacial complex. Because the changes tend to be symmetric, the effect may not be clinically obvious; cephalometric analysis may be used to delineate the extent of the condition.

7.8 Dental caries

Dental caries are often a consequence of radiation-induced xerostomia. Caries susceptibility is not limited to teeth within the radiation field. The harmful impact on post-radiation caries is as follows.[64,174,177-179]

The gradual fall of salivary pH, the reduced volume and altered composition of saliva, combined with its reduced lubricating and cleansing activity, result in adherence and stagnation of both saliva and food debris around the teeth and the emergence of a highly cariogenic microflora (*Streptococcus mutans* and *Lactobacillus* species), increasing the vulnerability to decay.

7.8.1 Dental Caries Management

Treatment strategies should be directed to each component of the caries process.[180] Optimal oral hygiene should be maintained. Caries resistance can be enhanced via use of topical fluorides [180] and/or remineralizing agents. Use of topical fluoride has demonstrable benefit in minimizing caries formation. Daily application of fluoride is recommended.[181-184] Efficacy of topical products may be enhanced by increased contact time on the teeth by application using custom trays. Fluoride mouth trays should be used judiciously to avoid exacerbation of pre-existing mucositis. Patients not able to effectively comply with use of fluoride trays should be instructed to use brush-on gels and rinses.

Cultural data can be useful in defining level of risk in relation to colonization patterns. Topical fluorides or chlorhexidine rinses may lead to reduced levels of Streptococcus mutans but not Lactobacilli.[185,186]

Remineralizing agents which are high in calcium phosphate and fluoride have demonstrated salutary in vitro and

clinical effects.[187] The intervention may be enhanced by delivering the drug via customized vinyl carriers. This approach extends the contact time of active drug with tooth structure which leads to increased uptake into enamel.

7.9 Periodontal disease

Dental plaque is the primary etiological agent in the development of periodontal disease. Plaque accumulates on the teeth, then initiates an inflammatory response causing erythema and edema.[188]

Periodontal tissues directly in the radiation field may be significantly damaged displaying disorganization of ligamentous fibres, thickening of membranes, and loss of vascularity reducing the capacity for repair and regeneration and probably accounting for the resultant mobility and/or loss of teeth. Periodontal disease involves inflammation but is not painful, unless the patient develops an acute periodontal abscess.

7.10 Neurologic disorders

Chemotherapeutic agents may have a toxic effect on peripheral and autonomic nerves and, on occasion, cranial nerves are affected. Such complications include pain, which mimics that of dental or periodontal origin and paresthesia to the head and neck region. Plant alkaloids such as vincristine or vinblastine are most commonly associated with these neurotoxic effects. Dental hypersensitivity in patients may occasionally arise weeks or months following discontinuation of chemotherapy.

Selected patients may experience spontaneous or induced pain of the temporomandibular joint. This condition is not unique to cancer patients, and may be associated with stress and dysfunctional habits including bruxism and clenching of the jaws.

7.11 Fatigue and Frustration

Cancer patients undergoing high dose chemotherapy and/or radiation can experience fatigue related to either disease or its treatment.[189] These processes can produce sleep deprivation or metabolic disorders, which collectively contribute to compromised oral status. In addition, patients receiving intensive treatments may become tired, frustrated with the treatment, or run out of motivation. The fatigued and/or frustrated patient may have difficulty complying with mouthcare protocols. Biochemical abnormalities may also be present. It is still important that the patient makes every reasonable effort to continue their mouth care, despite the concurrent fatigue.

It is important to support the patient during the periods of fatigue and frustration. Reassurance that the feelings are normal and that it will improve in time should be balanced with gentle but firm encouragement to continue the mouth care practices even when the patient seems to have no energy. Involvement of the family to help perform mouth care practices may be particularly important during periods of fatigue (and pain).

7.12 Taste Alteration

Taste alteration comprises a reduction in taste sensitivity (hypogueusia), an absence of taste sensation (ageusia), or a distortion of normal taste (dysgueusia). These symptoms are usually transient, but may be permanent and can lead to food aversion, nausea, and vomiting.[190-196]

Taste is mediated through organs known as taste buds, which are essentially found on the tongue (in papillae) and are continuously renewed. The number of papillae and taste buds diminish with age. Free nerve endings in the epithelium of the mouth also mediate taste sensation.

Attenuation or loss of the sense of taste and smell is commonly associated with radiation therapy. Radiation affects taste by damaging the taste buds and by modifying saliva. The taste buds alone are relatively resistant to radiation damage. However, the changes in saliva and oral mucosa seriously modify the patient's ability to taste even though taste buds are nearly normal. The perception of sour and bitter are suppressed more than that of sweet and salty.

Alteration in taste in cancer patients may be correlated with the location or extent of the tumor, independent of the histological type. There is an association between advanced disease and an abnormality in the recognition of sugar and urea for example.

Causes of taste alteration

1. Local disease of the mouth and tongue caused by cancer
2. Partial glossectomy
3. Damage to the nervous structure following surgery or cerebral lesions
4. Alteration of the cell renewal, or cell regeneration cycle
   - Malnutrition
   - Metabolic disturbances
   - Ionizing radiation
   - Medications
   - Endocrine factors (thyroidectomy, hypophysectomy, adranalectomy)
   - Viral infections
   - Reduced saliva
5. Modification in the receptor cells due to alteration of saliva by metabolic agents, medicine, and/or radiation
6. Dental pathology
7. Poor dental hygiene

7.13 Dysgueusia

Dysgeusia is the presence of a chronic taste in the mouth (often bitter, salty or metallic). This very unpleasant taste sensation may be an adverse effect from some cancer treatment medications, and it may affect eating and nutrition. The reduced taste threshold for bitter taste often results in cancer patients removing meat from their diet (source of urea, which produces a bitter taste). Patients may also have a raised threshold for sweet taste (i.e. less ability to taste sweet foods). A common report is an unpleasant metallic taste associated with

Table 7.8 Strategies to Maintain Nutrition in Patients with Oral Complications

- Inform patients of possibility of food aversion before starting treatment
- Avoid eating for up to 4 hours before and after chemotherapy or irradiation of the bowel
- Modify the texture and consistency of the diet
- Add between-meal snacks to increase protein and caloric intake
- Vitamin, mineral, and caloric supplements
- If tolerated, fruit juice before meals may stimulate the appetite
- Avoid rough, irritating food, citrus fruits, and extremes in food temperature- if stomatitis present
- Frozen confections can numb oral discomfort
- Determine what the patient is capable of swallowing- if dysphagia is present
- Soft, bland diet or liquids may be better tolerated than solid foods
- Increase fluid intake, unless contraindicated
- Provide continuing support to patient that their situation will improve over time

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chemotherapy, which may be worsened by placing metal in the mouth (e.g. metallic cutlery).

Zinc supplementation (zinc sulfate 220 mg, twice a day) has been reported to be useful in some patients, the overall benefit of this treatment remains unclear.

7.15 Nutrition

7.15.1 Nutritional deficiencies [197]

Nutritional deficiencies may develop as a result of oral discomfort associated with chemotherapy and/or radiation therapy complicated by mucositis, xerostomia, taste loss, dysphagia, nausea, vomiting, or anorexia.

Quality of life is compromised as eating becomes more problematic. Oral pain upon eating may lead to selection of foods that do not aggravate the oral tissues, often at the expense of adequate nutrition.

7.15.2 Nutrition Management

Best Practice Statement:

Maintenance of adequate nutrition may be compromised in patients with oral complications to cancer treatment. A referral to a dietitian should be considered for patients experiencing difficulties with eating during and after cancer treatment.

Nutritional deficiencies can be minimized by modifying the texture and consistency of the diet. If tolerated, patients can be encouraged to add between-meal snacks to increase protein and caloric intake. Dietary caloric supplements, with additional minerals and vitamins, may be added to the diet according to patient tastes, to further improve nutritional status. If tolerated, fruit juice before meals may stimulate the appetite. If patients can tolerate meats, sweet marinades or soy sauce can enhance their flavor. Increasing the use of spices, seasoning, and garlic can enhance taste, except for patients with dysgeusia. If stomatitis is present, patients should avoid rough, irritating food, citrus fruits, and extremes in food temperature. Eating frozen confections can numb oral discomfort. If dysphagia is present, determine what the patient is capable of swallowing. A soft, bland diet or liquids may be better tolerated than solid foods. Using creams and gravies also can make eating easier when pain is present. Patients may wish to avoid favorite foods during treatment, to avoid development of food aversions which may last beyond the treatment period. Increasing fluid intake, unless contraindicated, also can enhance taste.[198]

Nutritional counseling may be required during and following therapy with emphasis on maintenance of appropriate caloric and nutrient intake. Nasogastric (NG) or percutaneous esophageal gastrostomy (PEG) feeding tubes may be required when swallowing is significantly impaired.

When nutrition is seriously compromised due to mucositis or nausea, and NG or PEG tubes cannot be used, the physician may consider initiating IV hyperalimentation (TPN or total parenteral nutrition), which has been beneficial in many cases.
However, the hazards associated with this type of therapy (e.g. risk of infection from continuous indwelling IV line in an immunosuppressed patient) reinforce the importance of preventing mucositis, infection and hemorrhage in the patient receiving chemotherapy for cancer.[199]

7.17 Neutropenic ulcers

Mouth ulcers are a characteristic complication of severe neutropenia, usually occurring with neutrophil counts of less than $0.1 \times 10^9/L$ [182-184]. Neutropenic ulcers typically presents as one or more lesions characterized by regular margins,

a yellow/white background that is not easily removed, and few signs of inflammation. The clinical appearance of an ulcer corresponds with the breakdown in the continuity of the cell to neighboring epithelial cells. All regions of the oral cavity can be involved, whether keratinized or not.

7.18 Tissue necrosis

Ideal management of the head/neck radiation patient is centered in prevention, based on comprehensive oral care pre-radiation. The dentition, periodontium, periapices, and mucosa should be thoroughly examined by a dentist in order to identify oral disease, which should be eliminated prior to cancer therapy. Dentition exhibiting poor prognosis and which lie within high dose fields should be extracted prior to radiation therapy. Ideally, at least 7 to 14 days should be allowed for healing prior to initiation of radiation, though some have suggested up to 21 days. Surgical technique should be as atraumatic as possible and utilize primary wound closure.[200-202]

7.19 Osteoradionecrosis

Patients at high risk for necrosis of the bone (osteoradionecrosis [201-217]) include alcoholics, heavy smokers, and patients with chronically poor nutrition or poor oral hygiene. Radiation induces reductions in the number of viable osteoclasts and osteoblasts and a gradual development of obliterative endarteritis, compromising blood supply to the bone. Thus, the radiated tissue becomes hypovascular, hypocellular and hypoxic and the ability to replace even normal cellular loss is impaired. Spontaneous osteoradionecrosis (ORN) is not, therefore, unlikely and appears related to higher therapeutic radiation doses.

Although ORN may develop in the absence of any readily identifiable triggering factors, it may be exacerbated in the presence of caries, oral/systemic infection or xerostomia. It can arise from one month to many years after therapy. Susceptibility to ORN may continue throughout the lifetime of the patient, and performance of dental extractions, invasive periodontal procedures or other surgical procedures in irradiated areas should be avoided whenever possible.

Patients who develop osteoradionecrosis (ORN) should be comprehensively managed including elimination of trauma, avoidance of removable dental prosthesis if the denture bearing area is within the ORN field, assuring adequate nutritional intake, and discontinuation of tobacco and alcohol use. Topical antibiotics (e.g., tetracycline) or antiseptics (e.g., chlorhexidine) may

Table 7.9 Management of Osteoradionecrosis (ORN)

- Elimination of trauma
- Avoidance of removable dental prosthesis if the denture bearing area is within the ORN field
- Adequate nutritional intake
- Discontinue tobacco and alcohol use
- Topical antibiotics (e.g. tetracycline) or antiseptics (e.g. chlorhexidine) may contribute to wound resolution.
- Hyperbaric oxygen therapy (HBO).
- Surgical debridement of necrotic bone, as required.
- Partial mandibulectomy for severe cases of ORN

May be duplicated for use in clinical practice. As appears in: Broadfield L, Hamilton J. Best Practice Guidelines for the Management of Oral Complications from Cancer Therapy. © *Cancer Care Nova Scotia*, 2006

Table 7.10 Agents for Management of Oral Lesions in Chronic GVHD	
Topical Steroids	Rinses: dexamethasone elixir (Decadron®, generics). Gels, creams: • fluocinonide (Lyderm®, Tiamol®) • clobetasol • halobetasol (Ultravate™) • betamethasone (Lotriderm®, Diprosone®, Valisone-G®, others) Powders: beclomethasone (Beclovent®, Qvar™) (inhalers applied to mucosa)
Topical Immuno-suppressants	• azathioprine rinse (Imuran®; 5-8 mg/ml) • cyclosporin (Neoral®)
Antifungals	Systemic agents: • fluconazole (Diflucan®, generics) • itraconazole (Sporanox®) Topical preparations: • clotrimazole (Canesten®, others) • nystatin (Mycostatin®, generics) • amphotericin (Fungizone®)
PUVA	Psoralen and ultraviolet irradiation
Sialogogues	• pilocarpine (Salagen®) • bethanechol (Duvoid®)
Topical Anesthetics	• lidocaine (Xylocaine®, generics) • diphenhydramine (Benadryl®, generics OTC) • doxepin (Sinequan®, generics)

contribute to wound resolution. Wherever possible, coverage of the exposed bone with mucosa should be achieved; necrotic bone must be debrided before any attempt to cover the area with soft tissue, however. Analgesics for pain control are often effective. Surgical debridement of bone sequestrae may be necessary.

Hyperbaric oxygen therapy (HBO)[218,219] is generally recommended for management of ORN in that it increases oxygenation of irradiated tissue, promotes angiogenesis, and enhances osteoblast repopulation and fibroblast function. HBO is usually prescribed as 20 to 30 dives at 100% oxygen and 2 to 2.5 atmospheres of pressure. If surgery is needed, 10 dives of postsurgical HBO are recommended. Unfortunately, HBO technology is not always accessible to patients who might otherwise benefit.

Partial mandibulectomy may be necessary in severe cases of ORN. The mandible can be reconstructed to provide continuity for esthetics and function. In most cases, ORN is primarily managed by OMF surgery. A multidisciplinary cancer team including oncologists, oncology nurses, maxillofacial prosthodontists, general dentists, hygienists, and physical therapists may be involved in continuing management of these patients.

7.20 Mandibular dysfunction

Trismus of the muscles of mastication is a relatively common occurrence after head and neck radiation, due to induced hypovascularity and soft tissue fibrosis and scarring.

Patients can be instructed in physical therapy interventions including mandibular stretching exercises as well as use of prosthetic aids designed to reduce severity of fibrosis. It is important that these approaches be instituted prior to trismus development. If clinically significant changes develop, several approaches

including stabilization of occlusion, trigger point injection and other pain management strategies, muscle relaxants, and/or tricyclic medications can be considered.[218]

7.21 Osteonecrosis of the Jaw (ONJ)

It has been recognized in recent years that a syndrome of jaw osteonecrosis is associated with the use of bisphosphonates. Osteonecrosis of the jaw is not clearly defined, but may be described as an area of exposed bone that persists for 6 weeks or longer. Symptoms may range from none to severe jaw pain. ONJ is uncommon with low dose bisphosphonate therapy (used for osteoporosis prevention) but is more common with the intravenous bisphosphonates (e.g. pamidronate, zoledronic acid) used in cancer therapy[220].

ONJ can complicate regular dental procedures. Dentists should include questions to screen for bisphosphonate use in cancer patients seen for any dental care. If a patient is receiving a bisphosphonate agent, dental extractions should be avoided. If dental surgery is indicated, endodontic procedures, such as root filling treatment should be considered instead of extraction. If extraction is not avoidable, this procedure must include minimal trauma to the bone and soft tissue flap raising[220].

There are no guidelines to date on management of ONJ, but management recommendations include consideration of topical (e.g. chlorhexidine, tetracycline) and systemic broad-spectrum antibiotics, good oral hygiene, surgical management of exposed bone (if possible) and protection of exposed bone. There is no evidence whether discontinuation of the bisphosphonate will help, although it may be helpful to plan routine oral examinations by the community dentist for patients prescribed bisphosphonate therapy[221].

7.22 Graft-versus-Host Disease

Allogeneic hematopoietic stem cell transplantation patients (receiving stem cells from a donor) are at risk for graft-versus-host disease (GVHD).[222-224] GVHD may begin with engraftment (usually 14 days after transplant). Mucosal erythema and erosion/ulceration are typical symptoms of acute GVHD. Chronic GVHD, which begins day 100 of the transplant, may include long-term oral complications.[225] Oral lesions in chronic GVHD are similar to those in acute GVHD, but may also include raised white plaques and striae, increased involvement of the lips, and persistent reduced salivary function. Oral symptoms of GVHD, both acute and chronic, may include xerostomia and increased sensitivity and pain with spices, alcohols, and flavoring agents (especially mint flavors in toothpaste and oral care products). Oral GVHD has also been linked with oral precancerous and malignant lesions.[226]

Diagnosis of oral GVHD may be established by biopsy of the oral mucosa (including surface epithelium and minor labial salivary glands).[227-229] Presence of a lymphocytic infiltrate (grade I) with epithelial cell necrosis (grade II) provides the diagnostic basis for oral GVHD. Clinical criteria for oral signs and symptoms of GVHD may also be used for diagnosis, which may eliminate the need for a diagnostic oral biopsy unless the clinical examination is not sufficient for diagnosis.

Systemic therapy with steroids, cyclosporine and other immunosuppressive agents remains the foundation for treatment of oral GVHD

symptoms. Patients with clinically significant xerostomia may benefit from pilocarpine (5 mg 3 or 4 times a day) if salivary gland function remains at least partially intact. Topical management of oral mucosal lesions in graft-versus-host disease (GVHD) may include steroids, azathioprine, and/or oral psoralen and ultraviolet A (PUVA) (see Table 5.7).[226,230] Topical cyclosporin has been used for management of oral lesions, but it has proven to be less effective and much more expensive than other options. Likewise, topical use of other drugs used for reduction of graft rejection, such as tacrolimus and mycophenolate mofetil, have not proven to be efficacious.

A related condition referred to as pseudo-GVHD may also occur with autologous hematopoietic stem cell transplant patients. The oral lesion often mimics naturally occurring autoimmune diseases such as erosive lichen planus, lupus erythematosus, scleroderma and Sjögren's syndrome.

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